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Proposed Registration Document PRD2014-13

Ethaboxam

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Overview

Proposed Registration Decision for Ethaboxam

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Ethaboxam Technical and Intego Solo Fungicide, containing the technical grade active ingredient Ethaboxam, to control or suppress major seed and seedling diseases caused by Oomycetes on cereal grains, legume vegetables and oilseed crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Ethaboxam Technical and Intego Solo Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on ethaboxam, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on Ethaboxam Technical, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Ethaboxam?

Ethaboxam is a new fungicide with systemic properties used in the formulation of Intego Solo Fungicide. Intego Solo Fungicide will be used as a seed treatment to control or suppress major seed and seedling diseases caused by Oomycetes on cereal grains, legume vegetables and oilseed crops.

Health Considerations

Can Approved Uses of Ethaboxam Affect Human Health?

Intego Solo Fungicide, containing Ethaboxam Technical, is unlikely to affect your health when used according to label directions.

Potential exposure to ethaboxam may occur through the diet (food and water), or when handling and applying the end-use product Intego Solo Fungicide, or when planting seeds treated with this product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

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[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

In laboratory animals, technical grade ethaboxam was of low acute toxicity by the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes, non-irritating to the skin, and did not cause an allergic skin reaction. Similarly, the acute toxicity of the end-use product, Intego Solo Fungicide, was low by the oral, dermal and inhalation routes of exposure. It was non-irritating to the eyes, minimally irritating to the skin, and did not cause an allergic skin reaction. Consequently, no hazard signal words are required on the labels.

Health effects in animals given repeated doses of ethaboxam included effects on the blood, liver, lungs and thymus, as well as on male reproductive organs and the spermatogenic cycle. Ethaboxam reduced fertility, and there was evidence that it interferes with cell division. There was no evidence to suggest that it interacts directly with DNA. Ethaboxam also caused testicular cell tumours in the rat. The immune system was adversely affected, as evidenced by decreases in thymus weight and effects on white blood cells. There was no indication that ethaboxam caused damage to the nervous system.

When ethaboxam was given to pregnant or nursing animals, effects on the offspring (birth defects, decreased survival and delayed maturation) were observed at doses that were toxic to the mother, indicating that the young do not appear to be more sensitive than the adult animal.

The risk assessment protects against the effects of ethaboxam by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and children 3-5 years old, the subpopulation which would ingest the most ethaboxam relative to body weight, are expected to be exposed to less than 1% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from ethaboxam is not of health concern for all population subgroups.

The lifetime cancer risk from the use of ethaboxam on Crop Group 6 (succulent and dried, except for cowpea and field pea), Crop Group 15 (except rice, sorghum, and wild rice), and Crop Group 20A is not of health concern.

Acute dietary (food plus drinking water) intake estimates for the general population and all population subgroups were less than 1% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was all infants (<1 year old).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

The uptake study on canola, corn, sorghum, wheat and soybeans, and soybean residue trials conducted in the United States, including Canadian representative growing zones, using ethaboxam are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Consultation Document.

Occupational Risks From Handling Intego Solo Fungicide

Occupational risks are not of concern when Intego Solo Fungicide is used according to the proposed label directions, which include protective measures.

Workers treating seed with Intego Solo Fungicide in commercial facilities, by commercial mobile systems and with on-farm seed treatment equipment, and workers planting Intego Solo Fungicide treated seed can come into direct contact with ethaboxam residues on the skin and through inhalation. Therefore, the label specifies that workers treating and handling treated seed must wear the following personal protective equipment (PPE). In commercial seed treatment facilities and for commercial mobile treaters, workers must wear a long-sleeved shirt, long pants, chemical resistant gloves, socks and shoes or boots during mixing, loading and application. In addition, coveralls are required during clean-up, maintenance and repair activities. Workers bagging, sewing, stacking or performing other activities not involving direct contact with treated seed must wear a long-sleeved shirt, long pants, gloves, socks and shoes or boots. At on-farm locations, workers must wear a long-sleeved shirt, long pants, chemical resistant gloves, socks and shoes or boots during mixing, loading, application, clean-up and repair and during planting of treated seed. Closed transfer is required for treating seeds in commercial seed treatment facilities and for mobile treaters. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals is not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Ethaboxam Is Introduced Into the Environment?

When used as a seed treatment, ethaboxam poses a negligible risk to terrestrial and aquatic organisms.

Ethaboxam can enter the environment by dislodging from treated seed surfaces during and after seeding. Once in the environment, ethaboxam breaks down quickly in soil but more slowly in water. It is unlikely to evaporate from soil or water. Ethaboxam has medium to low mobility in soil and has a low potential to leach to groundwater. Ethaboxam is not expected to reach surface waters in any appreciable amounts under the current use pattern, as exposure of surface waters through soil runoff and leaching is expected to be minimal. Risk to terrestrial and aquatic organisms is negligible based on low potential for exposure.

Value Considerations

What Is the Value of Intego Solo Fungicide?

Intego Solo Fungicide is a new mode of action seed treatment with systemic properties that controls or suppresses major seed and seedling diseases caused by Oomycetes on cereal grains, legume vegetables and oilseed crops. Intego Solo Fungicide provides growers with a valuable alternative to metalaxyl, for which resistance is well documented on various crops. The integration of Intego Solo Fungicide into pest management programs may contribute to delaying resistance development to existing products in pathogen populations.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Intego Solo Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with ethaboxam on the skin or through inhalation of spray mists, anyone mixing, loading and applying Intego Solo Fungicide must wear the following personal protective equipment: In commercial seed treatment facilities and for commercial mobile treaters, workers must wear a long-sleeved shirt, long pants, chemical resistant gloves, socks and shoes or boots during mixing, loading and application. In addition, coveralls are required during clean-up, maintenance and repair activities. Workers bagging, sewing, stacking or performing other activities not involving direct contact with treated seed must wear a long-sleeved shirt, long pants, gloves, socks and shoes or boots. At on-farm locations, workers must wear a long-sleeved shirt, long pants, chemical resistant gloves, socks and shoes or boots during mixing, loading, application, clean-up and repair and during planting of treated seed. Closed transfer is required for treating seeds in commercial seed treatment facilities and for mobile treaters.

Environment

Although the risk of ethaboxam exposure to aquatic organisms is negligible, a statement on the toxicity of ethaboxam to aquatic organisms is required on the product label based on its inherent toxicity.

Next Steps

Before making a final registration decision on ethaboxam, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

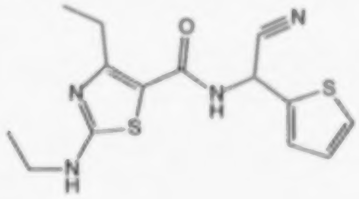
When the PMRA makes its registration decision, it will publish a Registration Decision on Ethaboxam (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Ethaboxam

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Ethaboxam
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(*RS*)-*N*-(α-cyano-2-thenyl)-4-ethyl-2-(ethylamino)-1,3-thiazole-5-carboxamide
2. Chemical Abstracts Service (CAS)	*N*-(cyano-2-thienylmethyl)-4-ethyl-2-(ethylamino)-5-thiazolecarboxamide
CAS number	162650-77-3
Molecular formula	$C_{14}H_{16}N_4OS_2$
Molecular weight	320.4
Structural formula	
Purity of the active ingredient	99.3 %

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Ethaboxam Technical

Property	Result
Colour and physical state	Pale brown or white powder
Odour	no significant odour
Melting range	decomposes at 185 °C
Henry's Law Constant	3.8×10^{-3} Pa.m^3/mole
Boiling point or range	not applicable

Density	1.28 g/mL
Vapour pressure at 20°C	8.1 x 10^{-5} Pa
Ultraviolet (UV)-visible spectrum	medium λ_{max}, nm neutral 231, 311 acidic 235, 284 basic 252, 335
Solubility in water at 20°C	solvent solubility (mg/L) purified water 4.8 pH 4 buffer 6.0 pH 7 buffer 5.2 pH 10 buffer 5.2
Solubility in organic solvents at 20°C	solvent solubility (g/L) n-heptane 0.00039 xylene 0.14 n-octanol 0.37 1,2-dichloroethane 2.9 ethyl acetate 11 methanol 18 acetone 40
n-Octanol-water partition coefficient (K_{OW})	pH log K_{OW} 4 2.73 7 2.89 10 2.91
Dissociation constant (pK_a)	(pKa) = 3.6 (for the conjugate acid of the amine)
Stability (temperature, metal)	Stable at elevated temperatures and in contact with metals and metal salts

End-Use Product—Intego Solo Fungicide

Property	Result
Colour	off white, opaque
Odour	Paint-like
Physical state	Liquid
Formulation type	SU (suspension)
Guarantee	Ethaboxam: 383 g/L
Container material and description	Plastic bottles, drums, jugs and totes
Density	1.10 – 1.14 g/mL
pH of 1% dispersion in water	7.6

Oxidizing or reducing action	Product does not contain oxidizing or reducing substances
Storage stability	Study not yet provided
Corrosion characteristics	Study not yet provided
Explodability	The product does not contain explosive ingredients

1.3 Directions for Use

Intego Solo Fungicide is to be applied as a seed treatment for control or suppression of various seed and seedling diseases on legume vegetables (19.6 mL/100 kg seed), oilseed crops from the rapeseed subgroup (13-19.6 mL/100 kg seed), corn (13-19.6 mL/100 kg seed) and other cereal grains (13-17 mL/100 kg seed).

1.4 Mode of Action

The mode of action of ethaboxam has been partially elucidated. The target site proposed by the Fungicide Resistance Action Committee is microtubule disruption. Microtubules are a component of the cell cytoskeleton. Disrupting their function affects fungal cell growth and morphogenesis.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Ethaboxam Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS) were developed and proposed for purpose of data generation (Method RM-49C) and enforcement (Method RM-49C-1) in plant matrices. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant matrices. The proposed enforcement method was successfully validated in plant matrices by an independent laboratory. Extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled crops was not required for the enforcement method.

There is currently no livestock method available for data gathering or enforcement purposes. An enforcement method for edible livestock commodities is not necessary, given that MRLs are not being proposed due to negligible potential for residue transfer to these matrices as a result of seed treatment uses. However, in the event that MRLs are required for livestock commodities due to the potential of residue transfer from a new use pattern, an adequate enforcement method for livestock commodities will be required. Methods for residue analysis are summarized in Table 1, Appendix I.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Ethaboxam is a thiazole carboxamide pesticide. The anti-fungal mode of action, which has been partially elucidated, involves disruption of microtubules, a cytoskeletal element that is critical for hyphal cell growth and fungal morphogenesis (Uchida et al. 2005). Microtubules play an equally critical role in mammalian cell division. It is unclear whether a similar mode of action occurs in mammalian cells, but a number of in vitro and in vivo effects in the ethaboxam toxicity database are consistent with this possibility.

A detailed review of the toxicological database for ethaboxam was conducted. The database consists of the full array of toxicity studies currently required for hazard assessment purposes. A waiver request was accepted in lieu of the required short-term inhalation toxicity study, based on low volatility, low acute inhalation toxicity, and a large margin for inhalation exposure. The database included a large number of in vitro and in vivo studies on the genomic toxicity of ethaboxam. There were also special mechanistic studies to investigate the proposed mode of action (MOA) for Leydig cell tumour formation. In addition, the acute and short-term oral toxicity, as well as the genotoxicity of the transformation product N-(cyano-thiophen-2-yl-methyl)-oxalamic acid (LGC-35523) were investigated.

Generally, the studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices (GLP). The scientific quality of the data is generally high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to ethaboxam.

Metabolism and toxicokinetics were investigated using thiazole- and thiophene-radiolabelled ethaboxam in single- and repeat-dose oral studies in the rat. Absorption was rapid and extensive, but was slightly sub-linear over the range of doses investigated. Peak concentrations in the blood occurred between 1 - 2 and 4 - 6 h post-dose at the low and high dose levels, respectively; the peak levels occurred later in females compared to males. Females also tended to have higher peak plasma concentrations (C_{max}) and greater systemic exposure than males. Most of the administered dose (AD) was eliminated within 48 h, regardless of the dose level. Approximately 23 - 30% of AD was recovered in the urine and 66 - 74% of AD was recovered in the feces after a single low dose. Biliary excretion was 51 - 63% of AD, accounting for a substantial proportion of the fecal excretion. Elimination via expired air was negligible. The elimination half-life ($t_{1/2}$) in the plasma was 31 - 41 h, while in blood cells it was substantially longer (69 - 162 h).

Although there were high levels of radioactive label in the thyroid at 5 days after dosing, overall there was no evidence of significant bioaccumulation. After a single dose, less than 0.8% of AD remained in the body at five days post-dose. With repeat dosing, tissue concentrations were 5 - 15-fold higher at five days post-dose, compared to the corresponding single-dose values. The absorbed radioactivity was widely distributed, with the highest tissue-specific radioactivity at five days occurring in the thyroid (thiazole label), liver, kidneys, blood cells and blood plasma in both sexes. Characterization of organ and tissue target sites was adequate, but it was not considered particularly robust, given that these data were obtained at 5-days post-dose, well after most of the radiolabel had been eliminated. The dosing regimen and the sex of the animal had no impact on either the distribution or elimination of ethaboxam.

Ethaboxam was metabolized extensively and the most prevalent transformation products were structurally similar to the parent chemical. Metabolic transformation involved N-deethylation followed by oxidation of the thiazole sulfur. Ethaboxam also underwent enolisation followed by either hydrolysis, or by sulphate conjugation with subsequent hydroxylation/sulphate conjugation. Regardless of the position of the radiolabel, the sex of the animal, or whether dosing was single or repeated, there were no major differences in the metabolite profile in rats. The parent chemical was a major fecal residue, accounting for 6 - 18% of the recovered label at the low dose and 47 - 68% at the high dose.

In the rat, the acute toxicity of ethaboxam and Intego Solo Fungicide was low by the oral, dermal and inhalation routes of exposure. Ethaboxam was minimally irritating to the eyes and non-irritating to the skin, whereas Intego Solo Fungicide was non-irritating to the eyes and minimally irritating to the skin in rabbits. Neither ethaboxam nor Intego Solo Fungicide caused skin sensitization in guinea pigs (Maximization and Buehler tests, respectively).

Overall, in repeated dose oral toxicity studies, modest decreases in body weight and body weight gain were observed in mice, rats, and dogs. In rodents, these body weight effects were more often accompanied by decreases in food conversion efficiency, than in food consumption. Ethaboxam had no obvious effect on palatability in any of the species investigated and there were no evident durational effects on the body weight changes. The liver also exhibited treatment-related changes in all species investigated, but a majority of the effects were considered adaptive, rather than adverse. There was very limited pathology in the liver, regardless of the dose, and only minimal evidence of a durational effect in mice, but not in rats or dogs. Dogs, but not rodents, were sensitive to short-term hematopoietic changes. Conversely, rodents, but not dogs, exhibited adverse pathological changes in the lungs. Compared to mice, lung effects in rats occurred at lower dose levels with short-term exposure. The rat was the most sensitive species investigated, and males were far more sensitive than females. This was due exclusively to the significant pathological effects that ethaboxam had on germ cells, spermatogenesis and the reproductive organs of males. With chronic dosing in male rats, these effects became more extensive and occurred at lower dose levels than in the short-term toxicity studies. Contrary to the studies conducted in rats, there were no evident effects of ethaboxam on male reproductive organs and spermatogenesis in dogs.

Following short-term oral dosing by capsule, dogs exhibited a range of hematopoietic changes. In males, there were decreases in several red blood cell parameters and an increase in extramedullary hematopoiesis in the spleen. Females exhibited thymic involution/atrophy and severe anemia. At higher dose levels males also exhibited thymic involution/atrophy, as well as decreased thymus weights. Females had an increased incidence of small thymus at the high dose. These short-term hematopoietic effects appeared to be transient, as they were not evident in dogs in the 1-year oral toxicity study.

In all species investigated, effects following short-term dietary dosing included increases in liver weight and hepatocellular hypertrophy. These effects were accompanied by increases in plasma cholesterol in rats and dogs, the two species in which this was measured. No other short-term pathological changes were observed in mice. With short-term dosing in rats, pathological changes were observed in the lungs and in male reproductive organs (discussed below) at the mid and high dose levels. The lung effects included increased lung weights and congestion, as well as increased incidences of focal alveolar septal congestion. At the high dose level, an increased incidence of focal alveolar hemorrhage also occurred. Similar changes were not evident at comparable dose levels in the reproductive toxicity or chronic toxicity/oncogenicity studies in rats, although lung changes were noted in males in the mouse oncogenicity study. Also following short-term dietary dosing at the high dose level in male rats, the adrenal glands were decreased in weight and exhibited increased fine vacuolation of the zona glomerulosa. Female rats had small uteri and/or fluid distension of the uterus, as well as increased hair loss at the high dose.

In male rats exposed to ethaboxam in the diet for 13 weeks, pathology in the reproductive organs was evident as decreased epididymal weights, and increases in the incidences of abnormal spermatids in the tubules of the testes as well as abnormal spermatogenic cells in the ducts of the epididymides. The effects were similar at similar dose levels in a separate 13-week special investigative dietary study of male rat genital tract pathology, but the histopathology also included increased cellular debris in the ducts of the epididymides and increased incidences of germ cell depletion/degeneration (unilateral or bilateral) in the testes. These histopathologic changes indicate that germ cells and spermatogenesis in rats are adversely affected following repeated dosing with ethaboxam. However, it is unclear whether the histological analyses conducted in these in studies were sufficiently sensitive to clearly identify the lowest dose level capable of adversely effecting spermatogenesis. While the onset of adverse effects on germ cells and the spermatogenic cycle is expected to be an immediate consequence of exposure to ethaboxam, the manifestation of any resulting histopathological change is expected to require time. Standard histological analyses may not be the most sensitive way to detect spermatogenic perturbation, particularly during its earliest stages. Analyses of sperm cell numbers, as well as their function and development (morphology), provide more direct, and potentially more sensitive, approaches for detecting spermatogenic defects.

There were a large number of additional effects on male reproductive organs observed at higher dose levels in the 13-week toxicity dietary studies in rats. At the high dose level in the testes there was severe atrophy, decreased organ weight, reduced numbers of spermatozoa, increased interstitial cell hyperplasia and increased numbers of multinucleated giant cells. In addition, there were increased incidences of testes that were small, flaccid, and/or blue. In the epididymides, there was increased inflammation and numbers of multinucleated giant cells, as well as increases in the incidences of small epididymides and absence of sperm. Finally, prostate and seminal vesicle weights were decreased. Concordant with these high dose changes in the male reproductive organs, there was a transient decrease in testosterone during the first 4 weeks of treatment. This effect recovered to control levels by week 13. In addition, luteinizing hormone (LH) and follicle stimulating hormone were both increased at week 13. Based on the higher dose-threshold for these hormone changes, they are considered secondary to other effects of ethaboxam on male reproductive organs.

With chronic dietary dosing, the suite of effects observed in the reproductive organs of male rats became further elaborated, more severe, and evident at lower dose levels than in the shorter-term studies, indicating a durational effect. Effects observed only after chronic dosing in rats included increased testicular atrophy and degeneration of the seminiferous tubules, increased epithelial vacuolation in the ducts and intraepithelial lumina of the epididymides, and reduced colloid in the prostate. All of these changes were observed at the LOAEL in the chronic dietary toxicity study. Effects observed at the LOAEL in the 13-week toxicity studies in rats, including small testes and decreased epididymal weights as well as absent or abnormal spermatozoa in the ducts of the epididymides, became evident in the chronic toxicity study at a dose level similar to the NOAEL established in the 13-week study. At the highest dose level in the dietary rat chronic toxicity study, most of the observed effects on male reproductive organs were already evident at 13 weeks. In addition to these shorter-term effects, males treated chronically at the high dose also exhibited small flaccid epididymides, acinar cell atrophy in the prostate, and seminal vesicle atrophy. In the high-dose females, focal acinar cell atrophy in the pancreas and hyperplasia in the pars distalis of the pituitary were observed.

In the dietary mouse oncogenicity study, effects observed after 78 weeks of dosing, including increases in liver weight and hepatocellular hypertrophy, remained evident at dose levels comparable to those at which such effects were observed in the 13-week study. Essentially, this same pattern was observed for body weight gain and food efficiency effects, but decreased body weight was also observed with chronic dosing in mice. Effects observed in male mice with chronic dosing, which were not observed in the shorter-term study in mice, included increases in the incidences of eosinophilic foci in the liver, as well as alveolar macrophage aggregations and perivascular lymphoid cells in the lungs.

In rats exposed to ethaboxam via the dermal route, there were systemic and local dermal effects after 28 days. The systemic effects included increased epithelial hyperplasia in male rats in areas of the skin that were not directly exposed to ethaboxam, and in females there were decreases in monocytes, large unstained cells and lymphocytes. There were no local dermal effects in females, but the treated skin in males exhibited increased epithelial hyperplasia, which was at times associated with hyperkeratosis, scabbing and/or dermal inflammation. At higher dose levels in males, the treated skin also exhibited ulceration. The potential for short-term inhalation effects was not evaluated for ethaboxam. Based on ethaboxam's low volatility, low acute inhalation toxicity, and a large margin for inhalation exposure, a data waiver request was accepted in lieu of the required short-term inhalation study.

Ethaboxam was tested for potential genotoxic activity in a battery of in vitro and in vivo assays. Based on uniformly negative results for the bacterial and mammalian mutagenicity studies, ethaboxam was not considered to cause DNA mutations. A large number of in vitro and in vivo chromosomal aberration studies were also conducted. There was no clear evidence from these studies that ethaboxam was clastogenic. However, in the in vitro studies using primary human lymphocytes, low concentrations of ethaboxam caused chromosomal non-disjunction and the formation of micronuclei via an aneugenic mechanism (gain or loss of whole chromosomes). At slightly higher concentrations, ethaboxam also potently inhibited the cell replication cycle (cytostasis). The adverse effects of ethaboxam on chromosomal sorting were difficult to detect in the in vitro chromosomal aberration assays because of ethaboxam's nearly dose-concordant cytostatic effects. The in vitro chromosomal effects became readily apparent only after the lymphocytes were permitted to recover for 28 hours following the exposure to ethaboxam. In a follow-up in vivo micronucleus test in mice treated intraperitoneally (i.p.), it was confirmed that micronucleated bone marrow reticulocytes were formed via an aneugenic mechanism. The post-exposure sampling time also appeared to be critical for in vivo detection of this effect, because the result was positive at 24 h after dosing, but not at 48 h. In this study, it was also demonstrated that systemic and bone marrow levels of ethaboxam were approximately dose-proportional, and that the maximal levels in the bone marrow were much higher than in the plasma. In mice dosed orally in a 5-day in vivo spermatogonial chromosomal aberration test, there was no evidence of clastogenicity; aneugenicity was not assessed. Spermatogonial chromosomal aberrations were not assessed in rats. However, in rats dosed orally, an in vivo bone marrow micronucleus test was negative for clastogenicity and aneugenicity. The achieved concentrations of ethaboxam in the spermatogonia of mice and in the bone marrow of rats were not quantified in either of these studies.

The mechanism of chromosomal non-disjunction and cell-cycle interruption in mammalian cells was not investigated in the ethaboxam toxicity database. Nevertheless, both of these effects are consistent with ethaboxam's known chemical MOA in fungi; the disruption of microtubule integrity. The mode of action of ethaboxam in mammalian cells was investigated in a mouse fibroblast cell line in a published study that focused on ethaboxam's mode of action in fungi (Uchida et al. 2005). In the mouse fibroblasts, there was no in vitro evidence of microtubule disruption at concentrations as high as 1 µg/mL. However, this observation is of limited insight into the mode of action of ethaboxam in mammalian cells. The highest concentration investigated in mouse fibroblasts in this published study was less than the lowest levels that had caused non-disjunction of chromosomes and the formation of micronuclei in primary human lymphocytes in the ethaboxam toxicity database (2 - 8 µg/mL). The mode of action responsible for in vivo effects on spermatogenesis and male reproductive organs is also not known, but it clearly includes impaired germ cell production as an early key event. The underlying cause of this impairment has not been investigated, but it is consistent with ethaboxam's cell cycle disrupting effects. Considering the primary toxicity effects of ethaboxam, an MOA involving the disruption of microtubule integrity is highly likely for mammalian cells.

In male rats in the 2-year chronic toxicity/oncogenicity dietary study, there was an increase in the incidence of testicular interstitial cell (Leydig cell) adenomas at the mid and high dose levels. The proposed MOA for the formation of this tumour type originates as an interruption of spermatid differentiation with consequent decreases in testosterone levels and concomitant increases in luteinizing hormone. Elevated LH levels stimulate Leydig cell proliferation. When LH stimulation is sustained over a prolonged period, increased Leydig cell proliferation can progress to hyperplasia and tumour formation. There was insufficient evidence to support this proposed MOA for Leydig cell tumour formation in male rats. Consequently, it was considered appropriate to use a linear low-dose extrapolation approach for the cancer risk assessment.

In female rats treated at the high dose, the incidence of pituitary adenocarcinomas exceeded the historical control range. There was increased hyperplasia at 52 weeks in the pars distalis of the pituitary, however, the incidences of pituitary adenomas and combined adenomas/adenocarcinomas were either within, or only slightly exceeded, the historical control ranges. There was also no evidence of a dose-response. In addition, higher mortality rates in treated females compared to the control group, suggests that the adenocarcinomas occurred at a dose level that may have exceeded the maximum tolerated dose (MTD) for females. For these reasons, there was low concern for this equivocal tumour response.

The reproductive toxicity of ethaboxam was assessed in rats treated via the diet in a range-finding and main study. In both studies, parental systemic toxicity was limited to decreases in body weight, body weight gain and food consumption at essentially the same dose level. In females in both studies, these effects tended to be more evident during the lactation period. In offspring in the main study, there were decreases in body weight and body weight gain as well as delayed sexual maturity in the presence of maternal systemic toxicity. At maternally toxic dose levels, offspring in the main study also exhibited decreases in litter size and offspring viability, as well as decreases in brain, spleen and thymus weights. In the range-finding study, in contrast to the main study, offspring body weight was decreased periodically during the lactation period (day 7 and 21), and spleen weights were also decreased, at a non-maternally toxic dose level. At the dose level where these offspring effects were observed, male reproductive toxicity in the range-finding study included decreased testicular sperm counts in F_0 males and decreased seminal vesicle weights in 7 week-old F_1 males. In contrast, there were no apparent reproductive toxicity effects in F_0 males in the main study at a comparable dose level, but some of the most relevant reproductive toxicity endpoints were not examined in the F_0 males in the main study (discussed below).

At the same dose level that produced systemic parental toxicity, reproductive effects in males were extensive and included the effects observed at comparable dose levels in the 90-day toxicity studies in rats. In addition, the sperm analyses in F_0 males in the range-finding study and in F_1 males in the main study revealed that there were decreases in normal sperm, sperm motility and progressive motility, as well as increases in decapitate and abnormal sperm. In addition, there were concordant decreases in epididymal sperm counts and histological evidence of reduced numbers of spermatozoa in the epididymides. In the testes, the complete depletion of germ cells was observed histologically. Overall, these effects indicate that male-specific reproductive toxicity at this dose level was well-developed and severe. At the same dose level as these male-specific effects, F_1 adults in the main reproductive toxicity study also exhibited an increased precoital interval and decreases in mating, conception and fertility. There were also decreases in implantation sites, the live birth index, and litter size at birth.

Despite the reported treatment-related effects occurring at the high dose level in F_0 males in the main reproductive toxicity study, sperm morphological analyses and histopathological assessments of the epididymides were not conducted at lower dose levels; under these circumstances, analyses at all dose levels are required by the OECD and OPPTS guidelines. In addition, only a subset of ten animals per group was examined for histological lesions in the F_0 generation. Based on OECD 416 guideline requirements, all F_0 males should have been examined histologically. Given the toxicological profile of ethaboxam, failure to conduct these analyses in the main reproductive toxicity study is considered a major limitation. Considering that germ cells in male rats exhibit evidence of an impaired cell cycle, it is possible that there is dose-concordant chromosomal toxicity (in other words, aneugenicity). Regardless, the male reproductive toxicity effects clearly represent the most sensitive endpoints in the ethaboxam toxicity database, and the most comprehensive assessment of such effects is normally conducted in the reproductive toxicity study. As a consequence of this major limitation, a NOAEL for reproductive toxicity in males could not be established. It is clear from the chronic toxicity study in rats that, after 1 year of exposure to ethaboxam, the treatment-related pathological changes in male reproductive organs became further elaborated, more severe, and occurred at a lower dose level than in the main reproductive toxicity study.

Two developmental toxicity studies were conducted by gavage in rats and a third such study was conducted in rabbits. In rats, based on the combined results of the two studies, decreases in litter and fetal weights became evident at the mid dose level. At higher dose levels in rats there were increased fetal incidences of abnormal lobulation of the liver, unossified sternebrae and total variant sternebrae. At the highest dose level investigated (limit dose), fetal animals had increased malformations (diaphragmatic hernia, misshapen pituitary) as well as increases in diaphragmatic, testicular and skeletal variations. In maternal animals at the mid dose level there were increases in dorsal hair loss/alopecia and water consumption. At higher dose levels in maternal animals there was increased post-dose salivation and decreased gravid uterine weight. Also, during the first two weeks of treatment, there were decreases in body weight gain and minimal decreases in food consumption. The decrement in body weight gain was greatest during the first two days of treatment and included body weight losses in a subset of dams. At the highest dose level investigated, maternal animals had decreased body weights and increased total resorptions. Considering the combined results, the developmental toxicity LOAEL in rats was based on decreases in litter and fetal weights, which occurred in the presence of maternal toxicity. In the rabbit study, no adverse systemic or developmental effects were observed in the fetal animals. Maternal toxicity occurred only at the highest dose level tested. The maternal effects consisted of transient losses in body weight during the first two days of treatment and decreased food consumption. In addition, there were two mortalities which followed a prolonged period in which food was not consumed; both of the affected animals were thin in appearance. There was no evidence in rats or rabbits that young animals were more sensitive to ethaboxam toxicity than the adult animal.

There were no gross or histopathological changes in either the central or peripheral nervous system in the acute and short-term neurotoxicity studies following oral exposure to ethaboxam. At the limit dose of 1000 mg/kg and higher in the acute oral neurotoxicity study, there were transient decreases in motor activity (rearing behaviour) in female rats on the first day of exposure, and at the highest dose level a number of animals exhibited altered breathing patterns and reduced levels of general arousal in the arena shortly after dosing. These changes observed shortly after dosing suggest that high doses of ethaboxam have a general systemic effect, rather than a specific neurotoxic effect. There was no evidence of neurotoxicity in the short-term oral neurotoxicity study in rats. In addition, there was very little evidence of neurotoxic potential in the broader toxicology database.

Ethaboxam did not adversely alter the immune system response as measured by the Jerne plaque-forming cell assay in rats in a 28-day oral immunotoxicity study. However, there was a treatment-related decrease in thymus weight at the high dose in this study, which was a recurring observation in the ethaboxam toxicity database. There were comparable effects on thymus weight in the range-finding immunotoxicity study in rats, in F_2 offspring in the main reproductive toxicity study in rats, and also in the 90-day dog study. In the dog study, there were also increased incidences of thymic involution, and small thymuses in females. In the dermal toxicity study in rats, there were decreases in several types of white blood cells. Based on these effects, ethaboxam is considered to adversely affect immune system organs, but only at relatively high dose levels.

The transformation product LGC-35523 (N-(cyano-thiophen-2-yl-methyl)-oxalamic acid) was of low acute toxicity and it had only minimal repeat-dose effects at the limit dose level in short-term dietary studies, which included decreases in food efficiency and also decreases in body weight and body weight gain in males. This transformation product did not cause mutations in bacterial assays or chromosomal aberrations in mammalian cells. Overall, LGC-35523 was considered no more toxic than the parent chemical.

Results of the toxicology studies conducted on laboratory animals with Intego Solo Fungicide are summarized in Table 3 of Appendix I, while those conducted with ethaboxam and the transformation product LGC-35523 are summarized in Table 2 of Appendix I. The toxicology endpoints for use in the human health risk assessment are summarized in Table 4 of Appendix I.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found in the Pesticides and Pest Management portion of Health Canada's website. Incidents were searched and reviewed for ethaboxam. Any additional information submitted by the applicant during the review process was considered. As of 7 February 2014, no health-related incidents involving ethaboxam were reported to the PMRA.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for ethaboxam. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a 2-generation reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of the young compared to parental animals in any of the studies. In the rabbit developmental toxicity study, there was significant maternal toxicity at the highest dose level, but no developmental toxicity was observed. In the rat reproductive toxicity study, the offspring exhibited decreases in body weight, organ weights, and viability during the lactation phase as well as delayed sexual maturation at the high dose. However, these effects occurred in the presence of significant systemic and reproductive toxicity in parental animals. In the rat developmental toxicity study, there was a serious effect on fetuses at the high dose level in the presence of maternal toxicity. There were increased incidences of malformations (diaphragmatic hernia, misshapen pituitary) in the presence of maternal toxicity (post-dose salivation, increased water consumption, alopecia, decreased gravid uterine weight and food consumption, body weight effects). In addition, there were other minor developmental effects (increased incidences of visceral and skeletal variations) in this study at the mid- and high-dose levels in the presence of maternal toxicity.

Overall, the database is adequate for determining the sensitivity of the young and effects on the young are well characterized. In the developmental and reproductive toxicity studies in rats, there was concern regarding the serious endpoints of malformations and reduced viability, respectively. However, in both studies the concern was tempered by the presence of maternal toxicity, suggesting that a 3-fold *Pest Control Products Act* factor would be required. Since the selected endpoints for risk assessment provide an intrinsic margin to the malformations, the *Pest Control Products Act* factor has been reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

General Population (including pregnant women, infants and children)

To estimate acute dietary risk (1 day), a developmental toxicity study in rats with a NOAEL of 100 mg/kg bw was selected for risk assessment. At the LOAEL of 300 mg/kg bw, a large decrement in body weight gain, including body weight losses in a sub-set of dams, was observed. These effects occurred following the first two days of dosing and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The composite assessment factor (CAF) is thus 100.**

The ARfD is calculated according to the following formula:

$$\text{ARfD (gen. pop)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{100 \text{ mg/kg bw}}{100} = 1.0 \text{ mg/kg bw of ethaboxam}$$

The ARfD provides a margin of 300 to the NOAEL for malformations that occurred in the presence of maternal toxicity in the developmental toxicity study in rats.

3.3 Acceptable Daily Intake (ADI)

To estimate risk following repeated dietary exposure, the chronic toxicity/oncogenicity study in rats with a NOAEL of 5.5 mg/kg bw/day was selected for risk assessment. At the LOAEL of 16.4 mg/kg bw/day, effects on germ cells, spermatogenesis, epididymal and testicular pathology, and reduced colloid in the prostate were observed. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The composite assessment factor (CAF) is thus 100.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{5.5 \text{ mg/kg bw/day}}{100} = 0.055 \text{ mg/kg bw/day of ethaboxam}$$

The ADI provides a margin of nearly 5,500 to the NOAEL for malformations in the developmental toxicity study in rats, and a margin of approximately 300 to the NOAEL for reduced viability in the reproductive toxicity study in rats. The ADI also provides a margin of slightly greater than 300 to the lowest dose level at which sperm effects were observed in the rat reproductive toxicity studies (range-finding).

Cancer Assessment

There was evidence of oncogenicity, based on an increased incidence of Leydig cell adenomas in male rats at the mid- and high-dose levels in the chronic toxicity/oncogenicity study. There was insufficient evidence available for ethaboxam to support a proposed non-genotoxic threshold-based MOA for the Leydig cell adenomas. Consequently, a linear low-dose extrapolation approach was used for the cancer risk assessment. A lifetime adjusted unit risk factor (q_1*) of 1.96×10^{-2} (mg/kg bw/d)$^{-1}$ was calculated for this tumour type. A q_1* was not calculated for the equivocal response of pituitary tumours in females at the high dose.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to ethaboxam is characterized as short- to intermediate-term in duration and is predominantly by the dermal and inhalation routes.

For short- and intermediate-term dermal and inhalation risk assessment for adults, the available 28-day dermal toxicity study did not address the endpoints of concern, namely effects on the male reproductive system, and a short-term inhalation toxicity was not provided, thus necessitating the use of an oral study for risk assessment. A NOAEL of 5.5 mg/kg bw/day from chronic toxicity/oncogenicity study in rats was selected. At 16.4 mg/kg bw/day in this study, toxicity was observed in males in the form of epididymal pathology (decreased weight, absent spermatozoa, abnormal spermatozoa, epithelial vacuolation in the ducts and intraepithelial lumina), testicular pathology (small testes, seminiferous tubule atrophy and degeneration) and prostate pathology (reduced colloid); a sub-set of comparable effects becomes evident at 13 weeks. There were no adverse effects in female rats at this dose level. Although the NOAEL selected is from a chronic study, there were no short- to intermediate-term studies that were considered to have comprehensively assessed the pathology and function of male reproductive organs. The NOAEL established in the 90-day toxicity study in rats was based on comparable relevant male reproductive toxicity endpoints, but did not include sperm analyses, which are considered potentially more sensitive indicators of early pathological change. The relevant male pathological effects were observed in the 2-generation reproductive toxicity study in rats, but a NOAEL could not established for males based on these observations because a major limitation was identified, as discussed in earlier sections. Although the chronic study did not include sperm analyses, this concern was tempered by the chronic duration of the study.

The target Margin of Exposure (MOE) for this endpoint is 100. Ten-fold uncertainty factors were applied each for interspecies extrapolation and intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

A rat dermal absorption study was submitted to support the registration of Intego Solo Fungicide. No major limitations were identified and its use to refine the dermal exposure values was supported. The apparent dermal absorption is 11%, from the low dose group (2 μg/cm^2) sacrificed at 120 hours. This value was calculated as the most conservative value from the total amount directly absorbed (excreta and carcass) plus the amount left in and around the dose site skin (treated skin fur, epidermal treated skin, stratum corneum, skin surrounding the dose site) which appeared to be potentially absorbable. The skin washes totaled 89% with a 99% recovery of the applied radioactivity.

3.4.2 Occupational Exposure and Risk

Crop Group 15: Cereal Grains (except rice, sorghum and wild rice), Crop Group 6: Legume Vegetables (succulent or dried except cowpea and field pea) and Crop Group 20A (rapeseed subgroup) can be treated with Intego Solo Fungicide in commercial seed treatment facilities and by commercial mobile treaters, and planted using conventional seeding equipment. Crop Group 15: Cereal Grains (except corn, rice, sorghum and wild rice) and Crop Group 6: Legume Vegetables (succulent or dried except cowpea and field pea) can be treated on-farm and planted using conventional seeding equipment.

3.4.2.1 Commercial Seed Treatment Exposure and Risk Assessment

Individuals have potential for exposure to ethaboxam while treating seed in commercial seed treatment facilities and by commercial mobile treaters. Chemical specific data for assessing human exposure during commercial seed treatment were not submitted. As such, surrogate exposure data were used to estimate risk to workers in commercial seed treatment settings.

3.4.2.1.1 Crop Group 15: Cereal Grains, Crop Group 6: Legume Vegetables and Crop Group 20A

Intego Solo Fungicide is for use by commercial seed treaters capable of treating cereal grain (including corn), legume and rapeseed seeds. Worker exposure was assessed for treating seeds with closed transfer systems only.

For assessing exposure during seed treatment in commercial operations, a surrogate passive dosimetry study measuring the exposure of mixers/loaders/calibrators (treaters), baggers/sewers/stackers and cleaners at 11 small to large commercial facilities treating cereal seed with Jockey Fungicide was used. Thirty seven trials were conducted with mixers, loaders, calibrators (7 operators) and baggers (22 operators) wearing a single layer and gloves and cleaners (8 operators) wearing coveralls over a single layer and gloves. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. Inhalation exposure for each worker was measured by means of a personal air sampling pump. Exposure values for treaters and baggers were normalized for the amount of active ingredient handled. Exposure values for cleaners were normalized to the application rate. The arithmetic mean was used for all activities since there were an adequate number of replicates and the recoveries were sufficient.

A seed treatment dust-off study was conducted to compare the dust-off potential of seeds treated with Intego Solo Fungicide with the dust-off potential of the seeds treated with other formulations that support the use of the surrogate study data. Seed treatment dust level evaluation (dust-off) experiments were conducted for untreated and treated canola, corn, soybean, wheat, barley and oat seeds. The study report concluded that dust-off potential of Intego Solo Fungicide treated canola, soybean and corn seeds are generally lower than that from surrogate test material-treated crops. Wheat seed dust-off was higher than that for corn, canola and soybean in all cases but generally lower than dust-off for barley and oats.

Seed treating capacities were derived from commercial throughput values for corn, soybean, canola and wheat. These representative crops are expected to be the largest amount treated commercially in Canada and are not likely to underestimate treating capacities for the other seed types identified on the label. Soybean values were used to cover Crop Group 6 seeds, canola values were used to cover Crop Group 20A seeds, wheat values were used to cover small grain Crop Group 15 seeds and corn values were used for corn seeds.

Table 3.4.2.1.1A presents the risk estimates for the commercial seed treatment of canola, corn, soybean and wheat seeds with Intego Solo Fungicide. The calculated MOEs were above the target MOE of 100. No occupational risks of concern were identified for ethaboxam exposure for treating cereal grain, corn, legume and rapeseed seeds commercially with Intego Solo Fungicide in closed transfer commercial facilities when workers wear the PPE worn in the surrogate study.

Table 3.4.2.1.1A Exposure & risk estimates for workers in commercial seed treatment facilities applying Intego Solo Fungicide

A. Cereal grain seed (barley, buckwheat, millet, oats, rye, teosinte, triticale, wheat)						
Scenario		**Unit Exposure**		**Exposure[2,5] (mg/kg bw/day)**		**MOE[4]**
		Dermal	**Inhalation**	**Dermal[3]**	**Inhalation**	**Combined**
Single layer, gloves	**kg a.i. handled/day[1]**	**ug/kg a.i. handled**				
Treater	5.98	0.88	0.016	0.00000726	0.00000120	652,000
Bagger/Sewer/ Stacker		17.67	0.89	0.000145	0.0000665	26,000
Coveralls over single layer, gloves	**g a.i./100 kg seed**	**ug/g a.i./100 kg seed**				
Cleaner	6.5	18.46	0.64	0.000165	0.0000520	25,300
Cleaner + Treater[6]		n/a	n/a	0.000172	0.0000532	24,400
B. Corn (field, sweet, popcorn)						
Scenario		**Unit Exposure**		**Exposure[2,5] (mg/kg bw/day)**		**MOE[4]**
		Dermal	**Inhalation**	**Dermal[3]**	**Inhalation**	**Combined**
Single layer, gloves	**kg a.i. handled/day[1]**	**ug/kg a.i. handled**				
Treater	9.375	0.88	0.016	0.0000113	0.00000188	416,000
Bagger/Sewer/ Stacker		17.67	0.89	0.000228	0.0000104	16,600
Coveralls over single layer, gloves	**g a.i./100 kg seed**	**ug/g a.i./100 kg seed**				
Cleaner	7.5	18.46	0.64	0.000190	0.0000600	22,000
Cleaner + Treater[6]		n/a	n/a	0.000202	0.0000619	20,900
C. Legumes (soybean, succulent or dried except cowpea and field pea)						
Scenario		**Unit Exposure**		**Exposure[2,5] (mg/kg bw/day)**		**MOE[4]**
		Dermal	**Inhalation**	**Dermal[3]**	**Inhalation**	**Combined**
Single layer, gloves	**kg a.i. handled/day[1]**	**ug/kg a.i. handled**				
Treater	4.725	0.88	0.016	0.00000572	0.000000945	826,000
Bagger/Sewer/ Stacker		17.67	0.89	0.000115	0.0000526	32,900
Coveralls over single layer, gloves	**g a.i./100 kg seed**	**ug/g a.i./100 kg seed**				
Cleaner	7.5	18.46	0.64	0.000190	0.0000600	22,000
Cleaner + Treater[6]		n/a	n/a	0.000196	0.0000609	21,400
D. Rapeseed (canola varieties only, cultivars, varieties, and/or hybrids of these)						
Scenario		**Unit Exposure**		**Exposure[2,5] (mg/kg bw/day)**		**MOE[4]**

		Dermal	**Inhalation**	**Dermal**[3]	**Inhalation**	**Combined**
Single layer, gloves	**kg a.i. handled/day**[1]	**ug/kg a.i. handled**				
Treater	5.025	0.88	0.016	0.00000608	0.00000101	776,000
Bagger/Sewer/ Stacker		17.67	0.89	0.000122	0.0000559	30,900
Coveralls over single layer, gloves	**g a.i./100 kg seed**	**ug/g a.i./100 kg seed**				
Cleaner	7.5	18.46	0.64	0.000190	0.0000600	22,000
Cleaner + Treater [6]		n/a	n/a	0.000196	0.0000610	21,400

[1] kg a.i. handled per day = kg seed treated per day × application rate (kg a.i./kg seed).

[2] For treater and bagger/sewer/stackers:

$$\text{Exposure (mg/kg bw/day)} = \frac{\text{Unit exposure (µg/kg a.i. handled per day)} \times \text{kg a.i. handled per day}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$$

[3] Dermal exposure adjusted for 11% dermal absorption.

[4] Dermal and inhalation NOAEL = 5.5 mg/kg bw/day; target MOE= 100

[5] For cleaning personnel, unit exposures are normalized for application rate (the highest application rate proposed was used) therefore:

$$\text{Exposure (mg/kg bw/day)} = \frac{\text{Unit exposure (µg a.i./g a.i./100 kg seed)} \times \text{application rate (g a.i./100 kg seed)}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$$

Dermal exposure adjusted for 11% dermal absorption.

[6] Cleaner task was < 1 hour per day therefore it was assumed other tasks such as treating may be performed.

A cancer quotient (q_1*) was identified and, therefore, a cancer risk assessment was required for occupational exposure. Cancer risk is estimated by extrapolating the average daily dose (ADD) over an average lifetime worked to obtain a lifetime average daily dose (LADD). The LADD is compared to the cancer risk quotient to determine the cancer risk. Corn data is shown as it represents the highest exposure per day of the proposed seeds and has the longest commercial treating period per year of the proposed crops. Individuals are expected to work a maximum of 206 days per year (maximum amount for corn) and may work up to 40 years in a commercial facility. A risk below 1×10^{-5} is generally considered acceptable in worker populations.

Table 3.4.2.1.1B presents the cancer risk estimates for the commercial seed treatment of corn seeds with Intego Solo Fungicide. No cancer risks of concern were identified for ethaboxam exposure for commercial treating of corn, cereal grain, legume and rapeseed seeds with Intego Solo Fungicide. Cancer risks for commercial treaters were all below 5×10^{-8}, below 1×10^{-6} for baggers and below 1×10^{-6} for cleaners.

Table 3.4.2.1.1B Cancer risk estimates for workers in commercial seed treatment facilities applying Intego Solo Fungicide

Corn							
Scenario		**Unit Exposure**		**ADD ^{2,4} (mg/kg bw/day)**		**LADD^{6} (mg/kg bw/day)**	**Cancer Risk^{7} (mg/kg bw/day)$^{-1}$**
		Dermal	**Inhalation**	**Dermal^{3}**	**Inhalation**		
Single layer, gloves	**kg a.i. handled/ day^{1}**	**ug/kg a.i. handled**					
Treater/ Applicator	6.75	0.88	0.016	8.17×10^{-6}	1.35×10^{-6}	2.76×10^{-6}	5×10^{-8}
Bagger/Sewer/ Stacker		17.67	0.89	0.000164	7.51×10^{-5}	6.92×10^{-5}	1×10^{-6}
Coveralls over single layer, gloves	**g a.i./100 kg seed**	**ug/g a.i./100 kg seed**					
Cleaner	7.5	18.46	0.64	0.000190	6.00×10^{-5}	7.25×10^{-5}	1×10^{-6}
Cleaner + Treater ^{5}		n/a	n/a	0.000199	6.14×10^{-5}	7.52×10^{-5}	1×10^{-6}

[1] kg a.i. handled per day = kg seed treated per day × application rate (kg a.i./kg seed).

[2] For treater/applicators and bagger/sewer/stackers:

$$\text{(ADD) (mg/kg bw/day)} = \frac{\text{Unit exposure (}\mu\text{g/kg a.i. handled per day)} \times \text{kg a.i. handled per day}}{80 \text{ kg bw} \times 1000\ \mu\text{g/mg}}$$

[3] Dermal exposure adjusted for 11% dermal absorption

[4] For cleaning personnel, unit exposures are normalized for application rate (the highest application rate proposed was used) therefore:

$$\text{ADD (mg/kg bw/day)} = \frac{\text{Unit exposure (}\mu\text{g a.i./g a.i./100 kg seed)} \times \text{application rate (g a.i./100 kg seed)}}{80 \text{ kg bw} \times 1000\ \mu\text{g/mg}}$$

[5] Cleaner task was < 1 hour per day therefore it was assumed other tasks such as treating may be performed.

[6] $$\text{LADD (mg/kg bw/day)} = \frac{\text{ADD x days of exposure per year x 40 years of exposure}}{\text{365 days x 78 years}}$$

[7] Cancer risk = LADD X q_1*; q_1* = 0.0196

3.4.2.2 On-Farm Seed Treatment Exposure and Risk Assessment

Individuals have potential for exposure to ethaboxam while treating seed on-farm. Chemical specific data for assessing human exposure during on-farm seed treatment were not submitted. As such, surrogate exposure data were used to estimate risk to workers treating seed on-farm.

3.4.2.2.1 Crop Group 15: Cereal Grains (Excluding Corn) and Crop Group 6: Legume Vegetables

Intego Solo Fungicide is intended for use with on-farm seed treaters capable of treating cereal grain (excluding corn) and legume seeds. Worker exposure was assessed for treating seed with open transfer systems.

For assessing exposure during seed treatment at on-farm operations, a previously reviewed surrogate passive dosimetry study measuring the exposure of treaters, baggers and cleaners on-farm treating cereal seed was used. Twelve workers were monitored during mixing, loading, applying, bagging and cleaning tasks while wearing a single layer and gloves. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. Inhalation exposure for each worker was measured by means of a personal air sampling pump. Exposure values were normalized for the amount of active ingredient handled per day. The 90th percentile was used for all activities since replicate numbers and field recoveries were low.

Seed treating capacities for on-farm treatment of legume and cereal seeds were derived from the PMRA default values. The amount handled for legume seeds (Crop Group 6) will be represented by the highest treated legume value, peas at 19,000 kg seed per day. The amount handled for small cereal seeds of Crop Group 15 will be represented by the maximum value for planting of wheat at 13,500 kg seed planted per day. These representative crops are expected to be the largest amount treated on-farm in Canada and are not likely to underestimate treating capacities for the other seeds types identified on the label.

Table 3.4.2.2.1A presents the risk estimates for the on-farm seed treatment of legume and small grain cereal seeds with Intego Solo Fungicide. The calculated MOEs were above the target MOE of 100. No occupational risks of concern were identified for ethaboxam exposure for treating small cereal grain and legume seeds on-farm with Intego Solo Fungicide with open transfer equipment when workers wear the PPE worn in the surrogate study.

Table 3.4.2.2.1A Exposure & risk estimates for workers treating seed with Intego Solo Fungicide on-farm

Crop	Amount handled[1] (kg a.i./day)	Unit Exposure (ug/kg a.i. handled)		Exposure[2] (mg/kg bw/day)		MOE[4]
		Dermal	Inhalation	Dermal[3]	Inhalation	
Legumes	1.4	142	7.83	0.000278	0.000139	13,200
Cereals	0.88	142	7.83	0.000171	0.0000859	21,400

[1] kg a.i. handled per day = kg seed treated per day × application rate (kg a.i./kg seed).

[2] Exposure (mg/kg bw/day) = $\frac{\text{Unit exposure (µg/kg a.i. handled per day)} \times \text{kg a.i. handled per day}}{80\ \text{kg bw} \times 1000\ \mu\text{g/mg}}$

[3] Dermal exposure adjusted for 11% dermal absorption.

[4] Dermal and inhalation NOAEL = 5.5 mg/kg bw/day; target MOE= 100

As in the commercial assessment, a cancer risk assessment was required for on-farm seed treatment. Individuals are expected to perform this task a maximum of 10 days per year and may work up to 40 years. A risk below 1 x 10^{-5} is generally considered acceptable in worker populations. No cancer risks of concern were identified for ethaboxam exposure for on-farm treating of cereal grain and legume seeds with Intego Solo Fungicide. Cancer risks for on-farm seed treating were below 1 x 10^{-7} for legumes and below 7 x 10^{-8} for cereals (Table 3.4.2.2.1B).

Table 3.4.2.2.1B Cancer risk estimates for workers treating seed with Intego Solo Fungicide on-farm

Crop	Amount handled[1] (kg a.i./day)	Unit Exposure (ug/kg a.i. handled)		ADD[2] (mg/kg bw/day)		LADD[4] (mg/kg bw/day)	Cancer Risk[5] (mg/kg bw/day)$^{-1}$
		Dermal	Inhalation	Dermal[3]	Inhalation		
Legumes	1.4	142	7.83	0.000278	0.000139	2.97 x 10^{-5}	1 x 10^{-7}
Cereals	0.88	142	7.83	0.000171	0.0000859	4.37 x 10^{-5}	7 x 10^{-8}

[1] kg a.i. handled per day = kg seed treated per day × application rate (kg a.i./kg seed).

[2] ADD (mg/kg bw/day) = $\frac{\text{Unit exposure (µg/kg a.i. handled per day)} \times \text{kg a.i. handled per day}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$

[3] Dermal exposure adjusted for 11% dermal absorption.

[4] LADD (mg/kg bw/day) = $\frac{\text{ADD x 10 days of exposure per year x years of exposure}}{\text{365 days x 78 years}}$

[5] Cancer risk = LADD X q_1*; q_1* = 0.0196

3.4.2.3 Planting Exposure and Risk Assessment

Individuals have potential for exposure to ethaboxam while planting treated seed. Chemical specific data for assessing human exposure during planting of treated seeds were not submitted. As such, surrogate exposure data were used to estimate risk to workers planting treated seed.

3.4.2.3.1 Crop Group 15: Cereal Grains, Crop Group 6: Legume Vegetables and Crop Group 20A

Intego Solo Fungicide treated cereal, corn, legume and rapeseed seeds may be planted on farms in Canada. Worker exposure was assessed for planting ethaboxam treated seeds with an open cab planter.

For assessing exposure during planting ethaboxam treated seeds, a previously reviewed surrogate passive dosimetry study that measured the exposure of workers loading and planting treated seed and during cleaning tasks was used. Thirteen workers were monitored during loading and planting and during cleaning tasks while wearing a single layer and gloves. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. Inhalation exposure for each worker was measured by means of a personal air sampling pump. Exposure values were normalized for the amount of active ingredient handled per day. The arithmetic mean was used for all activities as replicate numbers and field recoveries were sufficient.

Seed planting capacities for cereal, corn, legume and rapeseed seeds were derived from the PMRA default values. The amount planted per day for each crop group was chosen by selecting the crop within each group that has the maximum amount of seeds planted per day on average. The amount planted per day for legumes came from pea planting (19,000 kg seed/day), the amount for cereals came from wheat planting (13,500 kg seed/day), the amount for oilseeds came from canola (600 kg seed/day) and the amount for corn is 1,350 kg seed/day. These representative crops are expected to be the largest amount planted in Canada and are not likely to underestimate planting amounts for the other seeds types identified on the label.

Table 3.4.2.3.1A presents the risk estimates for the planting of ethaboxam treated rapeseed, corn, legume and small grain cereal seeds. The calculated MOEs were above the target MOE of 100. No occupational risks of concern were identified for ethaboxam exposure for planting seeds treated with Intego Solo Fungicide with open cab planting equipment when workers wear the PPE worn in the surrogate study.

Table 3.4.2.3.1A Exposure & risk estimates for planting Intego Solo Fungicide treated seed

Scenario	Unit Exposure (µg/kg a.i. handled)		kg seed planted per day	App. Rate (kg a.i./kg seed)	kg a.i. handled per day[1]	Exposure[2] (mg/kg bw/day)		MOE[4]
	Dermal	Inhalation				Dermal[3]	Inhalation	Combined
Oilseed	12,580	250	600	0.000075	0.045	0.000778	2.43×10^{-6}	7,040
Corn	12,580	250	1,350	0.000075	0.10125	0.00175	5.47×10^{-6}	3,130
Legume	12,580	250	19,000	0.000075	1.425	0.0246	7.70×10^{-5}	222
Cereal	12,580	250	13,500	0.000065	0.8775	0.0152	4.74×10^{-5}	361

[1] Kg a.i. handled per day = kg seed planted per day × application rate (kg a.i./kg seed).

[2] Exposure (mg/kg bw/day) = $\frac{\text{Unit exposure (µg/kg a.i. handled per day)} \times \text{kg a.i. handled per day}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$

[3] Dermal exposure adjusted for 11% dermal absorption.

[4] Dermal and inhalation NOAEL = 5.5 mg/kg bw/day; target MOE= 100

A cancer risk assessment was required for planting treated seeds. Individuals are expected to plant seed for 10 days per year typically and may work for 40 years on a farm. A risk below 1×10^{-5} is generally considered acceptable in worker populations. Cancer risks for planting were all below 7×10^{-6} (Table 3.4.2.3.1B). No cancer risks of concern were identified for ethaboxam exposure for planting seeds treated with Intego Solo Fungicide.

Table 3.4.2.3.1B Cancer risk estimates for workers planting seed treated with Intego Solo Fungicide

Crop	Amount handled[1] (kg a.i./day)	Unit Exposure (ug/kg a.i. handled)		ADD[2] (mg/kg bw/day)		LADD[4] (mg/kg bw/day)	Cancer Risk[5] (mg/kg bw/day)$^{-1}$
		Dermal	Inhalation	Dermal[3]	Inhalation		
Oilseed	0.045	12,580	250	0.000778	2.43×10^{-6}	1.10×10^{-5}	2×10^{-7}
Corn	0.10125	12,580	250	0.00175	5.47×10^{-6}	2.47×10^{-5}	5×10^{-7}
Legume	1.425	12,580	250	0.0246	7.70×10^{-5}	0.000347	7×10^{-6}
Cereal	0.8775	12,580	250	0.0152	4.74×10^{-5}	0.000214	4×10^{-6}

[1] Kg a.i. handled per day = kg seed treated per day × application rate (kg a.i./kg seed).

[2] ADD (mg/kg bw/day) = $\frac{\text{Unit exposure (µg/kg a.i. handled per day)} \times \text{kg a.i. handled per day}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$

[3] Dermal exposure adjusted for 11% dermal absorption.

[4] LADD (mg/kg bw/day) = $\frac{\text{ADD x 10 days of exposure per year x 40 years of exposure}}{\text{365 days x 78 years}}$

[5] Cancer risk = LADD X q_1*; q_1* = 0.0196

3.4.2.4 On-Farm Treating and Planting Exposure and Risk Assessment

Individuals have potential for exposure to ethaboxam while treating seeds on-farm with subsequent planting of the treated seeds in a single day.

3.4.2.4.1 Crop Group 15: Cereal Grains, Crop Group 6: Legume Vegetables and Crop Group 20A

Intego Solo Fungicide is proposed for on-farm use with cereal and legume seeds. As such, farmers are able to treat and plant treated seeds in a single day. Exposures from on-farm treating (Table 3.4.2.2.1A) were combined with exposures from planting (Table 3.4.2.3.1A). Calculated

MOEs were above the target MOE of 100 (Table 3.4.2.4.1A). No risks of concern were identified for ethaboxam exposure for on-farm treating and planting of cereal grain and legume seeds treated with Intego Solo Fungicide.

Table 3.4.2.4.1A Risk estimates for farmers treating and planting Intego Solo Fungicide treated seed

Crop	On-Farm Exposure (mg/kg bw/day)		Planting Exposure (mg/kg bw/day)		MOE[1]
	Dermal	Inhalation	Dermal	Inhalation	
Legume	0.000278	0.000139	0.0246	7.70 x 10^{-5}	219
Cereal	0.000171	0.0000589	0.0152	4.74 x 10^{-5}	355

[1] Dermal and inhalation NOAEL = 5.5 mg/kg bw/day; target MOE= 100

MOE = NOAEL / (on-farm dermal and inhalation exposure + planting dermal and inhalation exposure)

Average daily doses from on-farm treating (Table 3.4.2.2.1B) were combined with ADDs from planting (Table 3.4.2.3.1B). The combined on-farm treating and planting lifetime average daily dose was calculated to determine the cancer risk. Individuals who treat and plant on-farm are expected to do this activity for approximately 10 days per year typically and may work for up to 40 years. A risk below 1 x 10^{-5} is generally considered acceptable in worker populations. No cancer risks of concern were identified for ethaboxam exposure for on-farm treating and planting Intego Solo Fungicide treated seeds (Table 3.4.2.4.1B).

Table 3.4.2.4.1B Cancer Risk estimates for farmers treating and planting Intego Solo Fungicide treated seed

Crop	On-Farm ADD (mg/kg bw/day)		Planting ADD (mg/kg bw/day)		LADD[1] (mg/kg bw/day)	Cancer Risk[2] $(\text{mg/kg bw/day})^{-1}$
	Dermal	Inhalation	Dermal	Inhalation		
Legume	**0.000278**	**0.000139**	0.0246	7.70 x 10^{-5}	0.000353	7 x 10^{-6}
Cereal	**0.000171**	**0.0000589**	0.0152	4.74 x 10^{-5}	0.000218	4 x 10^{-6}

[1] LADD (mg/kg bw/day) = $\frac{(\text{on-farm ADD + planting ADD}) \text{ x } 10 \text{ days of exposure per year x } 40 \text{ years of exposure}}{365 \text{ days x } 78 \text{ years}}$

[2] Cancer risk = LADD X q_1*; q_1* = 0.0196

3.4.3 Residential Exposure and Risk Assessment

Bystander exposure should be negligible since the potential for drift is expected to be minimal when planting treated seeds.

3.5 Food Residues Exposure Assessment

3.5.1 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of ethaboxam in potential drinking water sources (groundwater and surface water) were generated using computer simulation models. The EECs of ethaboxam in groundwater were calculated using the PRZMGW model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using PRZMGW are based on the flux, or movement, of pesticide into shallow groundwater with time.

EECs of ethaboxam in surface water were calculated using the PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a small reservoir.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate, and using seed treatment. Table 3.5.1-1 lists the application information and main environmental fate characteristics used in the simulations. Twenty six of initial application dates between April and October were modelled. The model was run for 50 years for all scenarios. The largest EECs of all selected runs are reported in Table 3.5.1-2 below. Details of water modelling inputs and calculations are available upon request.

Table 3.5.1-1 Major groundwater and surface water model inputs for Level 1 assessment of ethaboxam

Type of Input	Parameter	Value
Application Information	Crop(s) to be treated	Barley, Beans, Borage, Buckwheat, Canola (rapeseed), Carinata, Chickpeas, Corn, Crambe, Cuphea, Echium, Flax seed, Gold of pleasure, Hare's ear mustard, Lentils, Lesquerella, Lunaria, Lupins, Meadowfoam, Milkweed, Millet, Mustard seed, Oats, Peas (succulent), Pigeon pea, Poppy seed, oil radish, Rye (fall and spring), Sesame19, Soybeans, Soybean (immature seed), Sweet rocket, Teosinte, Triticale and Wheat
	Maximum allowable application rate per year (g a.i./ha)	22.53
	Maximum rate each application (g a.i./ha)	22.53
	Maximum number of applications per year	1
	Method of application	Seed treatment
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	Stable
	Photolysis half-life in water (days)	4.46
	Adsorption K_{OC} (mL/g)	409.6 (20th percentile of 5 K_{OC} values for “chemical”)
	Aerobic soil biotransformation half-life (days)	5.2 (90th percentile confidence bound on mean of 4 half-life values adjusted to 25°C)
	Aerobic aquatic biotransformation half-life	51.9 (higher of two values)

Type of Input	Parameter	Value
	(days)	
	Anaerobic aquatic biotransformation half-life (days)	151 (only available value)

Table 3.5.1-2 Level 1 Estimated Environmental Concentrations of Ethaboxam in Potential Sources of Drinking Water

Pesticide	Groundwater (μg a.i./L)		Surface Water (μg a.i./L)	
			Reservoir	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Ethaboxam	0	0	1.2	0.15

[1] 90th percentile of daily average concentrations
[2] 90th percentile of yearly average concentrations
[3] 90th percentile of yearly peak concentrations
[4] 90th percentile of yearly average concentrations

3.5.2 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products and animal commodities is ethaboxam. The data gathering and enforcement analytical methods are valid for the quantitation of ethaboxam residues in crop matrices. The residues of ethaboxam are stable in soybean for up to 227 days when stored in a freezer at -20°C. Raw agricultural commodities were not processed due to the lack of quantifiable residues. Quantifiable residues are not expected to occur in livestock matrices with the current seed treatment use pattern. An uptake study on canola, corn, sorghum, wheat and soybeans, and soybean residue trials conducted in the United States, including Canadian representative growing zones, using end-use products containing ethaboxam at approved and exaggerated rates, are sufficient to support the proposed maximum residue limits.

3.5.3 Dietary Risk Assessment

Acute and chronic cancer and non-cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.16), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.3.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic non-cancer analysis for ethaboxam: 100% crop treated, default processing factors and residues of crop commodities based on MRL levels. The basic chronic dietary exposure from all supported ethaboxam food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 1% of the acceptable daily intake (ADI). Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to ethaboxam from food and drinking water is less than 1% (0.000101 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 3–5 years old at less than 1% (0.000231 mg/kg bw/day) of the ADI.

The refined chronic cancer risk assessment was conducted with the same criteria used for the chronic non-cancer assessment, except residues of crop commodities were based on half of the LOQ of the enforcement method, since residues were non-detectable in the uptake and crop field trial studies. The lifetime cancer risk from exposure to ethaboxam in food and drinking water was estimated to be 1×10^{-6} for the general population, which is not of health concern.

3.5.3.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for ethaboxam: 100% crop treated, default processing factors, residues in/on crop commodities at MRL levels. The basic acute dietary exposure (food alone) for all supported ethaboxam registered commodities for the total population, including infants and children, and all representative population subgroups is less than 1% of the ARfD. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that exposure is less than 1% (0.000286 mg/kg bw/day) of the ARfD for the general population. The highest exposure and risk estimate is for all infants (<1 year old) at less than 1% (0.000520 mg/kg bw/day) of the ARfD.

3.5.4 Aggregate Exposure and Risk

The aggregate risk for ethaboxam consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.5 Maximum Residue Limits

Table 3.5.5 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Crop Group 6 – Legume Vegetables (Succulent or Dried) (except cowpea and field pea)	0.02
Crop Group 15 – Cereal Grains (except rice, sorghum, and wild rice)	0.02
Crop Subgroup 20A – Rapeseed	0.02

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and Pest Management section of Health Canada's website.

For additional information on Maximum Residue Limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Tables 1, 5 and 7 in Appendix I.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on laboratory studies under aerobic conditions, ethaboxam is non-persistent in terrestrial environments and slightly persistent in water. Under anaerobic conditions, ethaboxam is moderately persistent to persistent in both media. In addition to aerobic biotransformation in soil and water, photolysis in water may be an important route of transformation near the surface of water bodies. Phototransformation on soil is not an important route of dissipation for ethaboxam. Hydrolysis is not an important route of transformation of ethaboxam in the environment. Ethaboxam is not expected to volatilize from water or moist soil. Ethaboxam has low to moderate mobility in soil and a low potential to leach through the soil column. Conservative water modelling of ethaboxam indicates that it is not expected to reach groundwater. No terrestrial field dissipation study was submitted for ethaboxam. Ethaboxam does not appreciably bioconcentrate in fish.

Transformation products LGC-32524, LGC-32533, LGC-32799 and 2-thiophene-carboxylic acid were major compounds in soil and were also formed in water as minor compounds, except for LGC-32799, which was only formed in the soil photolysis study. The major transformation product LGC-35525 and another major compound described as a carboxylic acid were formed in the aqueous photolysis study. In soil, all transformation products ultimately dissipated to relatively low concentrations. In water, transformation products tended to be stable or to dissipate more slowly, namely the major transformation products LGC-32533, LGC-35525, 2-thiophene-carboxylic acid and other minor transformation products. However, under the proposed seed treatment use patterns, because of the low application rates, the rapid dissipation of ethaboxam and its transformation products in soil, and their low potential to leach, they are not expected to reach aquatic systems in appreciable amounts. Future label expansions however, may trigger the need for further assessment of the transformation products in aquatic systems.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of the pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (that is, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the RQ is then compared to the level of concern (LOC = 1 for most species, 0.4 for pollinators and 2 for beneficial arthropods (predatory mite and parasitoid wasp)). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

Risk quotients for ethaboxam were calculated based on the highest maximum seasonal application rate for all uses, which is 7.51 g a.i./100 kg seed. The crop seeding rate resulting in the highest rate per hectare is for peas, at 22.53 g a.i./ha.

4.2.1 Risks to Terrestrial Organisms

A risk assessment for ethaboxam was conducted for terrestrial organisms. For acute toxicity studies, uncertainty factors of 1/2 and 1/10 the EC_{50} (LC_{50}) are used in modifying the toxicity values for terrestrial invertebrates, birds and mammals when calculating risk quotients (Table 11, Appendix I). No uncertainty factors are applied to chronic NOEC endpoints.

Ethaboxam is practically non-toxic to invertebrates, birds and mammals on an acute basis. Chronic toxicity was observed in birds and mammals, including reduced body weight (mammals) and reproductive impairment (birds and mammals). A summary of terrestrial toxicity data for ethaboxam is presented in Table 8 (Appendix I). The screening level risk assessment for ethaboxam is presented in Table 10 (Appendix I) for terrestrial organisms other than birds and mammals, and Table 12 (Appendix I) for birds and mammals.

Earthworms: Ethaboxam was not acutely toxic to earthworms. The risk quotient for earthworm resulting from acute exposure to ethaboxam does not exceed the level of concern at the screening level. The use of ethaboxam is expected to pose a negligible acute risk to earthworms.

Bees: Acute oral and contact exposure to ethaboxam did not result in treatment related mortality in adult honey bees. The resulting risk quotients for both acute contact and oral exposure routes were below the LOC, indicating ethaboxam is expected to pose a negligible risk to adult pollinators. Although a bee larval/brood toxicity study was not submitted, conservative estimates of exposure indicate that it is unlikely that a risk will be posed to bee larva through this use-pattern.

Beneficial arthropods: No toxicology studies on beneficial arthropods were submitted. As minimal exposure of ethaboxam to these species is expected under the current use pattern, such studies are not required at this time. They may be required for future label expansions.

Birds: Ethaboxam was not toxic to birds on an acute or dietary basis, with no treatment-related mortality, although sublethal effects such as decreased body weight gain, body weight and feed consumption were observed. Following reproductive exposure of the mallard duck, *Anas platyrhynchos*, to ethaboxam, reproduction was significantly affected at a concentration of 419 mg a.i./kg diet, equivalent to a daily dietary dose of 55 mg a.i./kg bw/day. The resulting NOEC was 170 mg a.i./kg diet, equivalent to 22 mg a.i./kg bw. To characterize the risk to birds, the likelihood of exceeding the toxic effects endpoints through feeding on treated seed was considered. The exposure of birds to a pesticide through consumption of treated seed is a function of the amount of pesticide on the seed, the body weight and food ingestion rate of the animal, and the number of seeds available for consumption. As an initial conservative screening level scenario, risk was characterized for generic small, medium, and large size classes of birds. For the screening level assessment, it was assumed that unlimited treated seed would be available for consumption over an extended time period and that 100% of the diet would consist of treated seed. In addition, the acute toxicity endpoints (acute oral and dietary) are divided by an uncertainty factor of 10 to account for potential differences in species sensitivity as well as varying protection levels (for example, community, population, individual). The risk quotients for birds resulting from acute or reproductive exposure to ethaboxam did not exceed the level of concern at the screening level. The use of ethaboxam as a seed treatment is expected to pose a negligible risk to birds.

Mammals: Ethaboxam was not toxic to mammals on an acute basis. However, a 2-generation reproductive toxicity oral dietary study conducted on rat resulted in offspring toxicity at 52.6/56.1 mg a.i./kg bw/day (♂/♀). The resulting NOEL was 16.2/17.6 mg a.i./kg bw/day (♂/♀). To characterize the risk to mammals, the likelihood of exceeding the toxic effects endpoints through feeding on treated seed was considered, in the same manner as described above for birds. The risk quotients for mammals resulting from acute, reproductive and developmental exposure to ethaboxam did not exceed the level of concern at the screening level. The use of ethaboxam as a seed treatment is expected to pose a negligible risk to mammals.

Vascular plants: No toxicology studies on vascular plants were submitted. As minimal exposure of ethaboxam to these species is expected under the current use pattern, such studies are not required at this time. They may be required for future label expansions.

4.2.2 Risks to Aquatic Organisms

A risk assessment for ethaboxam was conducted for freshwater and marine aquatic organisms based on available toxicity data, although minimal exposure is expected to these organisms based on the properties of this chemical and the current seed treatment use pattern. A summary of aquatic toxicity data is presented in Table 9 (Appendix I).

Similarly to the risk assessment for terrestrial organisms, for acute toxicity studies, uncertainty factors of 1/2 and 1/10 the EC_{50} (LC_{50}) are typically used for aquatic plants and invertebrates, and fish species, respectively, when calculating risk quotients (Appendix I, Table 11). No uncertainty factors are applied to chronic NOEC endpoints.

Ethaboxam was acutely toxic to invertebrates, fish, crustaceans and molluscs. Reproductive effects were also observed on invertebrates and clinical signs of toxicity were reported in early life stage studies on fish (Table 9, Appendix I). The screening level risk quotients for ethaboxam are summarized in Table 13, in Appendix I.

Invertebrates: Acute exposure to ethaboxam affected the survival of daphnids and marine crustaceans. Ethaboxam was also acutely toxic to mollusks, affecting the thickness of the shell deposition. Chronic exposure to ethaboxam affected the reproduction of daphnids at 0.1 mg a.i./L, with a resulting NOEC of 0.05 mg a.i./L. The risk quotients for freshwater and marine invertebrates resulting from exposure to ethaboxam do not exceed the level of concern at the screening level. The use of ethaboxam is expected to pose a negligible risk to freshwater and marine invertebrates. No toxicological studies on sediment-dwelling freshwater or marine invertebrates were submitted.

A chronic toxicity study on marine mysids was submitted but did not satisfy the guideline requirement, as toxicity endpoints could not be determined. As minimal exposure to ethaboxam is expected for aquatic organisms under this use pattern, further studies are not required at this time. They may however, be required for future label expansion.

Fish: Ethaboxam affected the survival of rainbow trout, *Oncorhynchus mykiss*, on an acute exposure basis, while it was not acutely toxic to fathead minnow, *Pimephales promelas*, at a concentration close to the limit of solubility nor to sheepshead minnow, *Cyprinodon variegates*, at a single limit concentration of 3.1 mg a.i./L. In contrast, effects on survival of fathead minnow were observed following early life-stage and short-term reproduction exposures at a concentration of 2.8 mg a.i./L, as well as clinical signs of toxicity in the surviving fry (NOEC of 0.88 mg a.i./L). These effects were also observed in a similar study conducted with sheepshead minnow at concentrations from 0.42 mg a.i/L and over (NOEC of 0.17 mg a.i/L). The risk quotients for freshwater and marine fish resulting from exposure to ethaboxam did not exceed the level of concern at the screening level. The use of ethaboxam as a seed treatment is expected to pose a negligible risk to fish.

Amphibians: The risk of ethaboxam exposure for amphibians was characterized at the screening level by comparing EECs in 15 cm water depth with the most sensitive fish toxicity endpoints used as surrogates for aquatic life-stages of amphibians. Risk quotients for amphibians resulting from acute or early life stage exposures to ethaboxam do not exceed the level of concern at the screening level. The use of ethaboxam as a seed treatment is expected to pose a negligible risk to amphibians.

Algae: Ethaboxam was not toxic to freshwater green algae, *Pseudokirchneriella subcapitata*, at concentrations up to 3.6 mg a.i./L. The risk quotient for freshwater algae resulting from acute exposure to ethaboxam does not exceed the level of concern at the screening level. The use of ethaboxam is expected to pose a negligible risk to freshwater algae. Toxicity studies with saltwater species were not submitted. As minimal exposure to ethaboxam is expected for aquatic organisms under this use pattern, studies are not required at this time. They may be required for future label expansion.

Aquatic vascular plants: No toxicology studies on aquatic vascular plants were submitted. As minimal exposure of ethaboxam to these species is expected under the current use pattern, such studies are not required at this time. They may be required for future label expansions.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

A total of 35 trials were provided in support of the proposed claims. Intego Solo Fungicide was tested against seed and seedling diseases of wheat (3 trials), corn (5 trials), soybean (8 trials), chickpea (7 trials), lentil (7 trials), pea (1 trial), snap bean (1 trial) and canola (3 trials). Scientific evidence included field, greenhouse and in vitro trials. In the majority of field trials, blanket treatments were applied on all seeds in order to prevent any confounding effects from early-season insect pests and/or fungal pathogens such as *Rhizoctonia* spp. and *Fusarium* spp.

5.1.1.1 Control of Seed Rot / Pre-emergence Damping-off Caused by *Pythium* spp. on Cereal Grains (except corn, rice, sorghum and wild rice)

Three field trials on wheat were provided in support of the proposed claim. In the one trial conducted under high disease pressure, Intego Solo Fungicide was tank-mixed with metconazole, but the latter was not included as a stand-alone treatment. Nevertheless, increasing rates of Intego Solo Fungicide from 5.0 to 13.0 mL/100 kg seed did result in a significant increase in plant emergence compared to the untreated control. Numerical increases in emerged seedlings were noted with Intego Solo Fungicide at 13.0 and 17.0 mL/100 kg seed in the two remaining trials, which were conducted under low disease pressure. Ethaboxam's efficacy against *Pythium* spp. on corn, soybean, chickpea, lentil and canola seeds was considered as supplementary evidence in support of the proposed claim. Based on similarities in seed size, seedling development and pest biology, extrapolation from wheat to cereal grains is considered adequate. Intego Solo Fungicide is supported at 13.0-17.0 mL/100 kg seed for control of seed rot / pre-emergence damping-off caused by *Pythium* spp. on cereal grains (except corn, rice, sorghum and wild rice).

5.1.1.2 Control of Seed Rot / Pre-emergence Damping-off Caused by *Pythium* spp. on Corn

Five field trials were provided in support of the proposed claim. In two of the five submitted trials, Intego Solo Fungicide at 13.0 and 19.6 mL/100 kg seed significantly increased plant emergence and yield in corn fields naturally infected with *Pythium* spp. In the three remaining trials, ethaboxam rates did not affect stand counts. The lack of statistical significance among treatments and variable stand counts noted in these studies are likely due to low disease pressure conditions. Ethaboxam's efficacy against *Pythium* spp. on wheat, soybean, chickpea, lentil and canola seeds was considered as supplementary evidence in support of the proposed claim. Intego Solo Fungicide is supported at 13.0-19.6 mL/100 kg seed for control of seed rot / pre-emergence damping-off caused by *Pythium* spp. on corn.

5.1.1.3 Control of Seed Rot / Pre-emergence Damping-off Caused by *Pythium* spp. on Legume Vegetables

Eight field trials were conducted on soybean (4 trials), chickpea (2 trials) and lentil (2 trials). The data package also included five greenhouse and two in vitro studies. Pathogen identity was not established in the soybean field trials. Consequently, they were considered as supplementary evidence, since seed rot symptoms could have been the result of infection from *Pythium* spp. or *Phytophthora sojae*.

Intego Solo Fungicide at 19.6 mL/100 kg seed consistently controlled seed rot / pre-emergence damping-off caused by *Pythium* spp. in the field, under moderate to high disease pressure. Intego Solo Fungicide was generally statistically comparable to Apron XL LS Fungicide with respect to plant emergence and yield. The fungicidal activity of ethaboxam against various *Pythium* species was confirmed in controlled environment studies. Ethaboxam's efficacy against *Pythium* spp. on wheat, corn and canola seeds was considered as supplementary evidence in support of the proposed claim. Based on similarities in seed size as well as crop and pest biology, extrapolation from soybean, chickpea and lentil to the legume vegetables is considered adequate. Intego Solo Fungicide is supported at 19.6 mL/100 kg seed for control of seed rot / pre-emergence damping-off caused by *Pythium* spp. on legume vegetables.

5.1.1.4 Suppression of Root Rot Caused by *Phytophthora sojae* on Soybean

Three field trials on soybean were provided in support of the proposed claim. Intego Solo Fungicide at 19.6 mL/100 kg seed provided at least suppression of seed rot / pre-emergence damping-off caused by *Phytophthora sojae* and improved seedling vigour in field trials. For example, in one trial from Ohio, the proposed rate improved stand counts by an average of 139% under high disease pressure. Such results were associated with substantial yield increases. Intego Solo Fungicide at 19.6 mL/100 kg seed provided numerically better emergence and yield than the lower tested rate of 17.0 mL/100 kg seed in certain soybean trials. The weight of evidence suggests that given its systemicity, Intego Solo Fungicide will reduce *Phytophtora* infections on soybean roots as well. Intego Solo Fungicide is supported at 19.6 mL/100 kg seed for suppression of early-season root rot caused by *P. sojae* on soybean only, as *P. sojae* is host-specific to this crop. Confirmatory value information is required to assess product efficacy on soybean roots.

5.1.1.5 Suppression of Root Rot Caused by *Aphanomyces euteiches* on Legume Vegetables

The challenges associated with generating field data on *Aphanomyces euteiches* were taken into consideration in the value assessment. Deleterious effects caused by this pathogen are generally observed in the field when populations have been built up for several years. Therefore, artificial inoculation with *A. euteiches* is not the favoured option for efficacy testing. Trials should be conducted in fields where susceptible crops have been grown for an extended period of time, which seldom occurs given that growers use resistant varieties and crop rotation.

Three field trials were conducted on chickpea, pea and snap bean. In addition, a total of four controlled environment studies (greenhouse and in vitro) were carried out on chickpea and lentil. The field trial on chickpea was not considered in support of the proposed claim, as artificial inoculation with *A. euteiches* was not successful. The field trial on pea was conducted under low disease pressure and product efficacy was not assessed on roots. Moderate disease pressure developed in the field trial on snap bean. Intego Solo Fungicide at 19.6 mL/100 kg seed significantly reduced root rot severity (rating: 3.6 on a 0-10 scale) compared to the untreated control (rating: 6.9) and the commercial standard Apron XL LS Fungicide (rating: 6.3). This level of protection corresponds to disease suppression. The fungicidal activity of ethaboxam on *A. euteiches* was confirmed in the submitted controlled environment studies.

Based on similarities in seed size, seedling development and pest biology, extrapolation from snap bean, chickpea and lentil to the legume vegetables is considered adequate. The weight of evidence supports the use of Intego Solo Fungicide at 19.6 mL/100 kg seed for suppression of early-season root rot caused by *A. euteiches* on legume vegetables. Intego Solo Fungicide is the first fungicide registered for this pest/crop combination in Canada.

5.1.1.6 Control of Seed rot / Pre-emergence Damping-off Caused by *Pythium* spp. on the Rapeseed Subgroup

Three field trials on canola were provided in support of the proposed claim. Adequate disease pressure developed in two of the three trials. Intego Solo Fungicide at 13.0 and 19.6 mL/100 kg seed provided notable increases in plant emergence and yield under moderate disease pressure. For example, in one trial from Ohio, treatments containing Intego Solo Fungicide at 13.0 and 19.6 mL/100 kg seed had 42.8 and 42.5 plants/row feet, respectively, which was statistically comparable to the commercial standard Apron XL LS Fungicide (41.5 plants/row feet) and Helix XTra Seed Treatment (45.3 plants/row feet). Ethaboxam's efficacy against *Pythium* spp. on wheat, corn, soybean, chickpea and lentil seeds was considered as supplementary evidence in support of the proposed claim. Based on similarities in seed size, seedling development and pest biology, extrapolation from canola to the rapeseed subgroup, including carinata, is considered adequate. Intego Solo Fungicide is supported at 13.0-19.6 mL/100 kg seed for control of seed rot / pre-emergence damping-off caused by *Pythium* spp. on the rapeseed subgroup.

5.2 Economics

No market analysis was performed for this application.

5.3 Sustainability

5.3.1 Survey of Alternatives

Refer to Table 15 of Appendix I for a summary of the active ingredients currently registered for the uses supported with Intego Solo Fungicide.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

Intego Solo Fungicide has shown to be compatible in a tank-mix with certain fungicide and insecticide seed treatments. When used as recommended, Intego Solo Fungicide would not interfere with the cultural and sanitation practices intended to prevent disease development in crops.

5.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

According to the Fungicide Resistance Action Committee , the risk of resistance development to this new active ingredient is currently unknown. No case of resistance has been reported at this time. Intego Solo Fungicide is to be applied preventatively to seeds and it is targeting low-risk soil-borne pathogens such as Pythium spp. and *Phytophthora sojae*, which limits the risk of resistance development.

5.3.4 Contribution to Risk Reduction and Sustainability

Intego Solo Fungicide provides growers with a valuable alternative to metalaxyl, for which resistance is well documented on various crops. The integration of Intego Solo Fungicide into pest management programs may contribute to delaying resistance development to existing products in pathogen populations.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, ethaboxam was assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

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[5] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

- Ethaboxam does not meet Track 1 criteria, and is not considered a Track 1 substance. See Table 14, Appendix I for comparison with Track 1 criteria.

- The identified major transformation products of ethaboxam, LGC-32524, LGC-32533, LGC-32799, LGC-35525 and 2-thiophene-carboxilic acid, were assessed against the Track 1 criteria by performing estimates of their log K_{ow} to assess their potential for bioaccumulation. All estimates were below the log K_{ow} of the parent, ethaboxam, and below the TSMP Track 1 criteria. Therefore, these transformation products are not considered to meet all Track 1 criteria.

- A log K_{ow} estimate could not be performed for another unidentified major transformation product. However, based on the data provided, it is not expected to be more bioaccumulative than ethaboxam or the other major transformation products. In addition, this compound was a major transformation product only in the aqueous photolysis study; with the properties of ethaboxam combined with the current seed treatment use pattern, ethaboxam and its transformation products are not expected to reach aquatic systems in significant amounts, minimizing the potential for the formation of this unidentified transformation product. Therefore, at this time, no further information is required for this unidentified major transformation product. However, confirmation data on its identity could be required for future label expansions.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

Technical grade ethaboxam and the end-use product Intego Solo Fungicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

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[6] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[7] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the New Pest Control Products Act.

[8] DIR2006-02, *Formulants Policy and Implementation Guidance Document y.*

The end-use product formulations also contains 1,2-benzisothiazoline-3-one, which contains low levels of polychlorinated dibenzodioxins and furans (TSMP Track 1). As the use of this preservative was recently re-evaluated and found to be acceptable (RVD2008-25), and because the input of dioxins into the environment from pesticides is being managed as outlined in the PMRA Regulatory Directive DIR99-03 for the implementation of TSMP, the Agency position is that no further action is required.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for ethaboxam is adequate to define the majority of toxic effects that may result from exposure. Ethaboxam is not selectively neurotoxic. In short-term and chronic studies on laboratory animals, the primary targets were the reproductive organs in male rats, the lungs, the blood and the thymus. Effects on white blood cells and the thymus were considered evidence of immunotoxicity. There was evidence of tumourigenicity in rats, but not in mice, after longer-term dosing. Serious effects (malformations, reduced viability) occurred in the young at doses that were toxic to the dams. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Workers treating seed with Intego Solo Fungicide and workers planting treated seed are not expected to be exposed to levels of ethaboxam that will result in an unacceptable risk when Intego Solo Fungicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is ethaboxam in plant products and in animal matrices. The proposed use of ethaboxam on Crop Group 6 (succulent and dried, except cowpea and field pea), Crop Group 15 (except rice, sorghum, and wild rice) and Crop Group 20A does not constitute a health risk of concern for chronic (cancer and non-cancer) or acute dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of ethaboxam.

Commodity	Recommended MRL (ppm)
Crop Group 6 – Legume Vegetables (Succulent or Dried) (except cowpea and field pea)	0.02
Crop Group 15 – Cereal Grains (except rice, sorghum, and wild rice)	0.02
Crop Subgroup 20A – Rapeseed	0.02

7.2 Environmental Risk

The use as a seed treatment of Intego Solo Fungicide containing the active ingredient ethaboxam is expected to pose a negligible risk to non-target terrestrial and aquatic organisms. No mitigation measures are required to further reduce the risk to the environment.

7.3 Value

The value information data submitted to register Intego Solo Fungicide is adequate to support the following claims:

- control of seed rot / pre-emergence damping-off caused by *Pythium* spp. on cereal grains (except corn, rice, sorghum and wild rice)
- control of seed rot / pre-emergence damping-off caused by *Pythium* spp. on corn
- control of seed rot / pre-emergence damping-off caused by *Pythium* spp. on legume vegetables
- suppression of early-season root rot caused by *Phytophthora sojae* on soybean
- suppression of early-season root rot caused by *Aphanomyces euteiches* on legume vegetables
- control of seed rot / pre-emergence damping-off caused by *Pythium* spp. on the rapeseed subgroup

8.0 Proposed Regulatory Decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Ethaboxam Technical and Intego Solo Fungicide, containing the technical grade active ingredient ethaboxam, to control or suppress major seed and seedling diseases caused by Oomycetes on cereal grains, legume vegetables and oilseed crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

^{14}C	carbon radionuclide with a molecular mass equal to 14
°C	degrees Celsius
♂	male
♀	female
↑	increase
↓	decrease
µg	micrograms
µM	micromolar
a.i.	active ingredient
abs.	absolute
AD	administered dose
ADD	average daily dose
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and excretion
ARfD	acute reference dose
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
bw	body weight
bwg	bodyweight gain
CAS	Chemical Abstracts Service
CAF	composite assessment factor
CEPA	*Canadian Environmental Protection Act*
C_{max}	maximum concentration
cm	centimetres
cm^2	square centimetres
CO_2	carbon dioxide
DAP	days after planting
DFOP	double first order in parallel
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{75}	dissipation time 75% (the dose required to observe a 75% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
ELISA	enzyme linked immunoassay
F_0	parental generation
F_1	first filial generation
F_2	second filial generation
fc	food consumption

fe	food efficiency
FISH	fluorescence in situ hybridization
g	gram
GD	gestation day
GI tract	gastrointestinal tract
GLP	Good Laboratory Practices
GSD	geometric standard deviation
h	hour(s)
ha	hectare(s)
hAR	human androgen receptor
HC	historical control
HCT	hematocrit
hERα	human estrogen receptor alpha
HGB	hemoglobin
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography – tandem mass spectrometry
HPLC-UVD	high performance liquid chromatography – ultraviolet detector
IORE	indeterminate order rate equation
i.p.	intraperitoneal
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
K+CWHR	kernel plus cob with husks removed
L	litre
LADD	lifetime average daily dose
LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LH	luteinizing hormone
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	low observed effect concentration
LOQ	limit of quantitation
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LSC	liquid scintillation counting
m^3	cubic meter
mg	milligram
mL	millilitre
$MAS_{24\text{-}72\,h}$	maximum average score for 24, 48 and 72 hours
MAS	maximum average score
MOE	margin of exposure
$MIS_{1\,h}$	maximum irritation score at 1 hour
mm	millimetre(s)

MRL	maximum residue limit
MMAD	mass median aerodynamic diameter
MOA	mode of action
MS	mass spectrometry
MTD	maximum tolerated dose
N/A	not applicable
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NZW	New Zealand white
OC	organic carbon content
OECD	Organisation for Economic Co-operation and Development
OPPTS	Office of Prevention, Pesticides and Toxic Substances
Pa	Pascal
PCE	polychromatic erythrocytes
PFC	plaque-forming cell
PHA	phytohemagglutinin
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
q_1*	lifetime adjusted unit risk potency factor for cancer
RBC	red blood cells
rel.	relative
RR	time interval between successive Rs of the QRS complex of the ECG wave
RQ	risk quotient
S9	microsomally-enriched sub-fraction isolated from rat liver
SC	soluble concentrate
SD	standard deviation
SFO	single first-order
SU	suspension
T	testosterone
$t_{1/2}$	half-life
t_R	representative $t_{1/2}$ from non-linear, multi-compartment kinetic models
TGAI	technical grade active ingredient
T_{max}	time of maximum concentration
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WBC	white blood cells
w/w	weight by weight basis

wc	water consumption
wk	week(s)
wt	weight(s)
WP	wettable powder

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Transition	Method Type	LOQ	Reference
Soil	LKF-114	parent	m/z 321 →200	HPLC-MS/MS	0.05 mg/kg in clay loam, sandy loam, and loamy sand soils	2111119 2111120
Sediment		extended from soil				
Water	LKF 115	parent	m/z 321 →200	HPLC-MS/MS	0.1 µg/L in ground and drinking water, 1.0 µg/L in surface and tap water	2111121 2111120
	263C-128		N/A	HPLC-UVD	40 µg/L in fresh and salt water	2138203
Biota	RM-49M	parent	m/z 321 →200	HPLC-MS/MS	0.02 ppm in chicken muscle	2204542
Plant	RM-49C	Ethaboxam		LC-MS/MS	0.01 ppm, Soybean seed, dry beans, wheat grain	2111252, 2204607
	RM-49C-1 (enforcement method)	Ethaboxam		LC-MS/MS	0.02 ppm, Wheat straw	2204607

Table 2 Toxicity Profile of Technical Ethaboxam and the transformation product LGC-35523

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted. Sex-specific NOAEL and LOAEL values, when established, are separated by a forward slash with the male value preceding the female value.)

Study Type/Animal/PMRA #	Study Results
Acute Toxicity Studies – Technical Ethaboxam	
Acute oral toxicity Sprague-Dawley rats PMRA #2111014	LD_{50} > 5000 mg/kg bw Low toxicity Clinical signs: ↑ drinking, urine, bright yellow urine; ↑ piloerection (♂); ↑ hair loss (♀)
Acute dermal toxicity Sprague-Dawley rats PMRA #2111016	LD_{50} > 5000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA #2111018	LC_{50} > 4.89 mg/L, MMAD = 4.25 µm, GSD = 2.34, 71% of particles considered respirable (≤ 7 µm) Low toxicity

Dermal irritation NZW Rabbits PMRA#2111020	MAS$_{24\text{-}72\text{ h}}$ = 0/8 (♂) Non-irritating
Eye irritation NZW Rabbits PMRA #2111019	MAS$_{24\text{-}72\text{ h}}$ = 0.2/110 (♂) Minimally irritating
Dermal sensitization (Maximization) Dunkin/Hartley Guinea pigs PMRA #2111021	Non-sensitizer (♂)
Metabolism and Toxicokinetic Studies – Technical Ethaboxam	
Metabolism/ Toxicokinetics, oral (gavage, single dose, 14-day repeat dosing, biliary excretion) Sprague-Dawley rats PMRA #2111096, 2111116, 2111117 ^{14}C-thiazole and ^{14}C-thiophene radiolabels	**Rate and extent of absorption and excretion:** Absorption of ethaboxam was rapid and extensive, but slightly sub-linear, over the range of doses investigated. Regardless of the radiolabel, peak concentrations in the plasma occurred within 1 to 6 hours of dosing, with peak times in females occurring later than in males. Females also had higher peak concentrations (C_{max}) and systemic absorption (AUC) than males (61 vs. 48% at 48 h, respectively). Repeated dosing resulted in higher values for C_{max} (1.2-1.3-fold), $t_{1/2}$ (1.2-1.9-fold) and AUC_{120} (~2-6-fold). Regardless of the dose level or radiolabel, most of the radiolabel was eliminated rapidly (within 48 h) via the feces (66-74% AD, single low dose), and to a lesser extent via the urine (23-30% AD, single low dose). At the high dose level, more excretion occurred via the feces than the urine, reflecting the lower relative absorption at this dose level. Whereas the biliary route was an important route of excretion (51-63% AD), only low levels of radioactivity (<0.7% AD) were eliminated via the expired air, regardless of the dose level. The elimination half-lives of radioactivity in plasma were 31-41 h, while in blood cells, $t_{1/2}$ values were substantially longer (69-162 h). Consistent with this, very low levels of radioactivity remained in the carcass after 5 days (<1-3% AD), indicating the retention was minimal. **Distribution / target organ(s):** Concentrations of radioactivity in tissues at 120 h following single or repeated low doses were generally highest in the thyroid (thiazole radiolabel only), liver, kidney, blood cells and whole blood. The tissue levels were 5-15-fold higher with repeated dosing, compared to those resulting from a single low dose. Overall tissue retention of radioactivity was low after single oral doses, accounting for <0.8% AD for both radiolabels and the different dose levels. **Toxicologically significant compound(s):** Ethaboxam was N-deethylated to form LGC-32794 (B22 & FE19) followed by oxidation of the thiazole sulfur to LGC-32800 (U17). Ethaboxam also underwent enolisation. In one pathway, the enol form underwent hydrolysis to the amide LGC-32801 (U13 & B15). In another pathway the enol underwent sulfate conjugation to LGC-32802 and hydroxylation/sulfate conjugation to LGC-32803. Unchanged ethaboxam (LGC-30473) was detected as a major component in fecal extracts at both dose levels (Low dose: 5.9-18.0% AD, High dose: 46.9-68.3% AD). Transformation products prevalent in the feces included LGC-32802 (3.4-10.8% AD), LGC-32803 (2.3-6.2% AD) and LGC-32801 (1.2-5.3% AD), regardless of the dose,

	radiolabel, or sex of the animal. The major radioactive component in urine was LGC-32801 (2.7-9.9% AD). All other urine metabolites represented <3% AD. The most prevalent biliary radioactive components were LGC-32801 and LGC-32794, which each represented <7% AD. In male rats, the profile of transformation products in the liver was similar to that of urine. There were no significant differences in the metabolite profiles of rats treated with the different radiolabels, or between sexes.
Short-Term Toxicity Studies – Technical Ethaboxam	
28-day, oral dietary, range-finding Sprague-Dawley rats PMRA #2351467	Supplemental **≥106/107 mg/kg bw/day:** ↓ bw, bwg, fe (♂) **≥301/301 mg/kg bw/day:** ↓ fe, ↑ rel. liver wt, ↑ alopecia; ↑ fur staining (♂); ↓ bw, bwg, fe, ↑ small uteri, minimal adipose tissue (♀) **440/456 mg/kg bw/day:** ↑ minimal adipose tissue, minimal seminal vesicle contents (♂); ↑ abs. thyroid wt; ↑ abs. liver wt, ↑ fur staining, ↑congested lungs (♀)
90-day oral dietary, range-finding CD-1 mice PMRA #2111023	Supplemental **≥74 mg/kg bw/day:** ↑ liver wt, ↑ liver centrilobular hepatocellular hypertrophy (♂) **≥163/195 mg/kg bw/day:** ↓ bwg, ↓ fe (♂); ↑ liver wt, ↑ liver centrilobular hepatocellular hypertrophy (♀)
90-day oral dietary Sprague-Dawley rats PMRA #2111022	NOAEL = 16.3/17.9 mg/kg bw/day LOAEL = 49.7/58.0 mg/kg bw/day **≥49.7/58.0 mg/kg bw/day:** ↑ lung wt, lung congestion, focal alveolar congestion; ↓ bw, bwg, fe, ↓ epididymides wt, ↑ abnormal spermatids in occasional tubules in testes, abnormal spermatogenic cells in the ducts of epididymides (♂); ↑ rel. liver wt (♀)
90-day oral capsule Beagle dogs PMRA #2111024	NOAEL = 15 mg/kg bw/day LOAEL = 40 mg/kg bw/day **≥40 mg/kg bw/day:** ↓ bw, ↓ bwg, ↓ RBC, HCT, HGB, ↑ extramedullary hematopoiesis in spleen; ↑ enlarged liver (♂); 1 animal at each dose level was euthanized prematurely due to severe anemia, ↑ hepatocellular hypertrophy, ↑ thymus involution/atrophy (♀)
52-week oral capsule Beagle dogs PMRA #2111026	NOAEL = 10 mg/kg bw/day LOAEL = 30 mg/kg bw/day **30 mg/kg bw/day:** ↓ bw, ↓ bwg
28-day dermal Sprague-Dawley rats PMRA #2111028	**Dermal toxicity** NOAEL = 100/1000 mg/kg bw/day LOAEL = 300 mg/kg bw/day / not established (♀) **≥300 mg/kg bw/day:** ↑ epithelial hyperplasia, sometimes with hyperkeratosis of the skin, scabbing, dermal inflammation (treated skin) (♂) **Systemic toxicity** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day **≥300 mg/kg bw/day:** ↑ epithelial hyperplasia (untreated skin) (♂); ↓ monocytes, large

	unstained cells, lymphocytes in the blood (♀)
28-day inhalation, waiver provided PMRA #2111029	Accepted, based on: • Low volatility • Low acute inhalation toxicity • Large extrapolated inhalation MOE
Chronic Toxicity/Oncogenicity Studies – Technical Ethaboxam	
78-week oral dietary CD-1 mice PMRA #2111030, 2111032-2111034	NOAEL = 35/44 mg/kg bw/day LOAEL = 117/135 mg/kg bw/day Survival (Week 78): ♂ 70%, 72%, 70%, 78%; ♀ 68%, 70%, 56%, 56% **117/135 mg/kg bw/day:** ↓ bw, ↓ bwg, ↓ fc, ↑ liver wt; ↑ centrilobular hepatocellular hypertrophy, ↑ liver eosinophilic foci, ↑ lung alveolar macrophage aggregations, ↑ lung perivascular lymphoid cells (♂) **No evidence of oncogenicity.**
104-week combined chronic/oncogenicity dietary Sprague-Dawley rats PMRA #2351470, 2111035	NOAEL = 5.5/21.0 mg/kg bw/day LOAEL = 16.4/45.5 mg/kg bw/day Survival (Week 104): ♂ 48%, 48%, 58%, 47%; ♀ 35%, 22%, 22%, 25% **≥16.4/21.0 mg/kg bw/day:** ↓ epididymis wt, ↑ small testes, ↑ seminiferous tubular atrophy in testis, ↑ seminiferous tubular degeneration in testis (slight), ↑ absent spermatozoa in epididymides, ↑ abnormal spermatogenic cells in the duct of epididymides, ↑ epithelial vacuolation in duct and intraepithelial lumina in epididymides, ↑ reduced colloid in prostate, ↑ **incidence of interstitial cell adenomas in testes (2, 7, 10, 12%; HC 0-6.2%, mean 2.5%)** (♂); ↑ cholesterol (non-adverse) (♀) **35.8/45.5 mg/kg bw/day:** ↑ cholesterol, ↓ seminal vesicle wt, ↑ small and flaccid epididymis & testes, ↑ blue testes and testicular masses, ↑ abnormal spermatogenic cells in duct, ↑ generalized or centrilobular hepatocellular hypertrophy, ↑ reduced number of spermatozoa in epididymides, ↑ acinar cell atrophy in prostate, ↑ seminal vesicle atrophy (♂); ↓bw, ↓bwg, ↓fc, ↑ focal acinar cell atrophy in pancreas, ↑ pars distalis hyperplasia in pituitary, ↑ depression from pituitary masses/enlarged pituitary (gross & histological), ↑ incidence of pars distalis adenoma + adenocarcinoma in pituitary (adenoma, 53, 65, 72, 60%, HC 56-70%, mean 63%); adenocarcinoma, 17, 15, 13, 25%, HC 2-15%, mean 10%; combined, 70, 80, 85, 85%, HC 68-82%, mean 73%) (Equivocal) (♀) **Evidence of oncogenicity (male interstitial cell adenomas in testes).**
Developmental/Reproductive Toxicity Studies – Technical Ethaboxam	
2-generation reproductive toxicity oral dietary (range-finding) Sprague-Dawley rats PMRA #2351471	**Supplemental** **Parental toxicity:** **≥57/58 mg/kg bw/day:** ↓ bw, bwg, fc (♂); ↓ bw, bwg, fc during lactation (♀) **≥87/87 mg/kg bw/day:** ↓ bw, bwg, fc during premating and gestation (♀) **Reproductive toxicity:** **≥18/18 mg/kg bw/day:** ↓ testicular sperm counts (F_0), ↓ seminal vesicle wt (F_1 7 weeks of age) (♂)

	≥57/58 mg/kg bw/day: ↓ % motile sperm, ↓ cauda epididymis wt, ↓ normal sperm morphology, ↑ decapitate sperm, ↑ abnormal sperm, ↑ abnormal spermatids in occasional tubules (♂); ↓ total and live litter size at birth (♀) **≥87/87 mg/kg bw/day:** ↓ cauda epididymal sperm counts, ↓ testis wt, ↓ epididymis wt (F_1), ↑ small, flaccid and dark testes, ↑ small epididymides (♂); ↑ pre-implantation loss (F_2 at GD 13), ↓ mean implantation sites, ↓ pups born live, ↓ fertility (1 or no litters produced), ↑ uterus and ovarian wts (♀) **Offspring toxicity:** **≥18/18 mg/kg bw/day:** ↓ bw (day 7 & 21 only at low dose), ↓ spleen wt (unselected F_1, day 22) **≥58 mg/kg bw/day:** ↓ live litter size during lactation (F_1) **≥87/87 mg/kg bw/day:** delayed vaginal opening (F_1) & preputial separation (F_1)
2-generation reproductive toxicity oral dietary Sprague-Dawley rats PMRA #2111050-2111052	**Parental toxicity** NOAEL = 16.2/17.6 mg/kg bw/day LOAEL = 52.6/56.1 mg/kg bw/day **52.6/56.1 mg/kg bw/day:** ↓ bw (F_0 ♂, F_1), ↓ bwg (F_1 ♂ premating, F_1 ♀ wk 1 pre-mating, F_0 ♀ LD 1-14, 1-21), ↓ fc (F_1) **Reproductive toxicity** **NOAEL and LOAEL values for male reproductive toxicity could not be established due to omitted F_0 male assessments of sperm morphology as well as histopathology of the testes and epididymides at low dose levels.** NOAEL = not established/17.6 mg/kg bw/day LOAEL = not established/56.1 mg/kg bw/day **52.6/56.1 mg/kg bw/day:** ↑ precoital interval (F_1), ↓ mating index (F_1), ↓ conception rate (F_1), ↓ fertility index (F_1); ↓ sperm motility & progressive motility, ↑ decapitate and abnormal sperm (F_1), ↓ normal sperm (F_1), ↓ cauda epididymis wt, ↓ epididymal sperm count (F_1), ↑ small epididymides (F_1), ↑ blue, flaccid and/or small testes (F_1), ↑ abnormal spermatogenic cells in epididymal ducts, reduced number of spermatozoa in epididymis (F_1), ↑ depletion of all germ cells in tubules of testis (F_1), ↑ abnormal spermatids in occasional tubules of testis (F_1) (♂); ↓ implantation sites (F_1), ↓ mean total and live litter size at birth (F_2), ↓ live birth index (F_2), prolonged gestation length (F_1) (♀) **Offspring toxicity** NOAEL = 16.2/17.6 mg/kg bw/day LOAEL = 52.6/56.1 mg/kg bw/day **52.6/56.1 mg/kg bw/day:** ↓ offspring viability index, ↓ mean live litter size throughout lactation (F_2), ↓ bw, ↓ bwg, delayed sexual maturation (F_1), ↓ terminal bw, ↓ abs. brain wt, ↑ rel. brain wt, ↓abs. spleen wt, ↓ abs. thymus wt (F_2) **Evidence of reproductive toxicity.** **No evidence of sensitivity of the young.**

Developmental, gavage (range-finding) Sprague-Dawley rats PMRA #2111067	Supplemental **Maternal toxicity** **≥100 mg/kg bw/day:** ↑ post-dose salivation, yellow staining (non-adverse) **≥300 mg/kg bw/day:** ↓ bwg (weight loss at high dose) **1000 mg/kg bw/day:** ↓ fc, ↑ wc **Developmental toxicity** **1000 mg/kg bw/day:** ↓ fetal wt No external malformations or variations observed.
Developmental, gavage Sprague-Dawley rats PMRA #2111066	**Maternal toxicity** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day Fetuses(litters) examined: 269(22), 276(22), 284(24), 261(21) **≥300 mg/kg bw/day:** ↑ post-dose salivation, ↑ wc, ↓ gravid uterine wt, ↑ yellow stained tray paper/fur **Developmental toxicity** NOAEL not established LOAEL = 100 mg/kg bw/day **≥100 mg/kg bw/day:** ↓ litter and fetal wts **≥300 mg/kg bw/day:** ↑ abnormal lobulation of the liver [fetuses(litters): 1(1), 5(3), 5(5), 9(7)], ↑ fetal incidences of unossified sternebrae and total variant sternebrae **1000 mg/kg bw/day:** ↑ malformations including diaphragmatic hernia [fetuses(litters): 0(0), 0(0), 0(0), 7(4)] & misshapen pituitary [fetuses(litters): 0(0), 0(0), 0(0), 6(2)], ↑ thin diaphragm with protrusion of the liver, ↑ displaced testes, ↑ incomplete ossification of one or more centres of the pelvic girdle, digits, sternebrae and thoracic vertebral centra, ↑ misaligned/bipartite sternebrae **Evidence of malformations.** **No evidence of sensitivity of the young.**
Developmental, gavage Sprague-Dawley rats PMRA #2111069	**Maternal toxicity** NOAEL = 30 mg/kg bw/day LOAEL = 100 mg/kg bw/day Fetuses(litters) examined: 232(18), 311(24), 268(23), 272(24), 287(23) **≥100 mg/kg bw/day:** ↑ dorsal hair loss/alopecia, ↑ wc **Developmental toxicity** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day

	≥300 mg/kg bw/day: ↑ abnormal liver lobulation [fetuses(litters): 2(2), 3(2), 2(2), 4(4), 7(5)] **No evidence of malformations.** **No evidence of sensitivity of the young.**
Developmental, gavage (range-finding) NZW rabbits PMRA #2111072	Supplemental **Maternal toxicity** **≥75 mg/kg bw/day:** ↑ orange coloured urine (non-adverse), ↑ inappetence, bw loss, ↓ fc **300 mg/kg bw/day:** 1 death (GD 19) preceded by inappetence and thin appearance, 2 additional ♀ were euthanized prematurely on GD 22 due to prolonged and severe inappetence (one aborted GD 20-21) **Developmental toxicity** **≥150 mg/kg bw/day:** ↓ fetal wt
Developmental, gavage NZW rabbits PMRA #2111071	**Maternal toxicity** NOAEL = 75 mg/kg bw/day LOAEL = 125 mg/kg bw/day Fetuses(litters) examined: 172(19), 133(17), 170(20), 137(16) **125 mg/kg bw/day:** ↑ premature euthanization/mortality in 2♀ (GD 15, 16; preceded by prolonged inappetence & thin appearance), ↑ bw loss (GD 6-8 with recovery thereafter), ↓ fc **Developmental toxicity** NOAEL = 125 mg/kg bw/day LOAEL not established No treatment-related changes were observed. **No evidence of malformations.** **No evidence of sensitivity of the young.**
Genotoxicity Studies – Technical Ethaboxam	
Bacterial reverse mutation PMRA #2111073	Negative
In vitro mammalian cell gene mutation Mouse lymphoma cells PMRA #2111077	Negative
In vitro mammalian chromosome aberrations	Unacceptable study (no replicate assay with clastogenic concentrations for 19 h treatment+S9)

Human lymphocytes PMRA #2111079	↑ chromosomal aberrations at ≥100 µg/mL ±S9, ↑ metaphase figures (mitotic index) at ≥250 µg/mL ±S9. Most frequently observed aberration was chromatid breaks suggesting a cytotoxic effect; concordant with necrotic cells and reduction in scoreable metaphase at ≥500 µg/mL.
In vitro chromosome aberration test, range-finding toxicity test using cytochalsin B Human lymphocytes PMRA #2111099	Supplemental **≥20 µg/mL:** ↑ cells at metaphase (up to 24-fold) **≥40 µg/mL:** ↓ binucleate cells (cytostasis)
In vitro micronucleus test, fluorescence in situ hybridization (FISH) staining Human lymphocytes PMRA #2111093	Positive Test 1: **15 µg/mL:** ↓ proliferation index (48 h PHA, –S9) **≥15 µg/mL:** Insufficient scorable dose levels (48 h PHA, -S9), insufficient toxicity at highest dose (24, 48 h PHA, +S9). **25 µg/mL:** ↓ proliferation index (24 h PHA –S9), **≥30 µg/mL:** Insufficient cells to score (non-viability) **50 µg/mL:** ↓ proliferation index (24 & 48 h PHA +S9) Test 2: **≥7.5 µg/mL:** ↑ non-viable cells (48 h PHA –S9) **10-20 µg/mL:** ↑ mononucleate & binucleate cells with micronuclei (24 h PHA –S9) **15 µg/mL:** ↓ proliferation index (48 h PHA –S9) **20 µg/mL:** ↓ proliferation index (24 h PHA –S9), ↑ non-viable cells (24 h PHA –S9), FISH positive (24 h PHA –S9); aneugenic mechanism **75 µg/mL:** ↓ proliferation index (24 & 48 h PHA +S9), ↑ non-viable cells (24 & 48 h PHA +S9), : ↑ mononucleate cells with micronuclei (24 h PHA +S9) Micronucleus analyses not done for 48 h PHA cultures, given that clear positive result occurred for the 24 h PHA cultures.
In vitro micronucleus test, FISH staining, non-disjunction Human lymphocytes PMRA #2111092	Positive (-S9 only, +S9 not investigated) NOEL: ~6-7 µg/mL for non-disjunction events measured via the use of chromosome specific DNA probes **≥8 µg/mL:** ↑ chromosomal loss and non-disjunction in binucleate cells **≥9 µg/mL:** ↑ mononucleate cells with micronuclei (48 h PHA) **≥10 µg/mL:** ↑ binucleate cells with micronuclei (48 h PHA)

	Evidence supports aneugenic mechanism for micronuclei formation
In vitro micronucleus test Human lymphocytes PMRA #2111094	Positive (-S9 only, +S9 not investigated) FISH positive (no non-disjunction in binucleate cells at 4 and 7 µg/mL) NOEL for mononucleate cells = 1 µg/mL (24 h PHA) & 2 µg/mL (48 h PHA) NOEL for binucleate cells = 4 µg/mL (24 h PHA) & 3 µg/mL (48 h PHA) Evidence supports aneugenic mechanism for micronuclei formation
In vivo micronucleus test, i.p. CD-1 mice PMRA #2111087	Suggestive, but no clear positive response (within HC). Bone marrow toxicity at the top two doses, and excessive toxicity at the top dose invalidate the micronucleus result at the top dose. **≥50 mg/kg bw/day**: underactive behaviour, piloerection, flattened posture, hunched posture, irregular respiration, partially closed eyelids, ungroomed coat **≥150 mg/kg bw/day:** ↓ PCE at 24 and 48 h, unsteady gait, writhing, ↓ bwg (days 2, 3) **300 mg/kg bw/day:** prostrate posture, slow respiration, cyanosis, thin build, 3 animals found dead (2 after 1st dose, 1 after 2nd dose), 1 animal euthanized as moribund at 46 h after 2nd dose Toxicokinetics & tissue-specific ethaboxam concentrations: 61 mg/L in plasma (T_{max}, 24 h), 597 mg/kg in liver (T_{max}, 24 h), 1051 mg/kg in spleen (T_{max}, 4 h) at 4 h, 246 mg/kg in testes (T_{max}, 2 h)
In vivo micronucleus test, FISH staining, i.p. CD-1 mice PMRA #2111083	Positive at 24 h (negative at 48 h) FISH analyses to determine whether induction of micronuclei due to aneugenicity or clastogenicity. **≥150 mg/kg bw/day:** ↓ body temperature (especially on Day 1), ↑ clinical signs (piloerection, ptosis, decreased activity, hunched posture, lethargy), ↓ bwg (days 1-3), ↓ reticulocytes (PCE) in bone marrow **300 mg/kg bw/day:** 2 mortalities, ↑ micronucleated reticulocytes in bone marrow (3 animals total) & peripheral blood (24 h); 80 or 90% of micronuclei centromere-positive (micronuclei due to whole chromosome loss; aneugenic mechanism), ↑ erythropoietin (24 h) Toxicokinetics & bone marrow-specific ethaboxam concentrations: Ethaboxam was rapidly absorbed via the i.p. route. Systemic exposure (plasma AUC) and exposure in bone marrow (AUC) increased in dose-proportional fashion (slope = 1.15- and 0.92-fold, respectively). Maximal levels in bone marrow (130-354 µg/g) occurred ~3 h post-dose (regardless of dose level) and were 11-29-fold higher than the maximal levels in plasma (12.2-24.7 µg/mL).

In vivo micronucleus test, oral gavage Sprague-Dawley rats PMRA #2111090	Negative **≥500 mg/kg bw/day:** abnormal gait, fast respiration, piloerection, flattened posture, underactivity, nervous behaviour, partially closed eyelids **2000 mg/kg bw/day:** 1 animal found dead (21 h post-dose), deep and irregular respiration, hunched posture, underactivity, nervous behaviour, coat & tail staining, ↓ bw (10%)
5-day in vivo chromosome aberration test in spermatogonia, oral gavage ICR mice PMRA #2111105, 2351477	Negative (aneugenicity was not assessed) No increase in the number of aberrant metaphases. No clinical signs except rough fur in all treated groups. **≥250 mg/kg bw/day:** Increased mitotic index considered evidence of exposure (tissue concentrations not quantified).
Neurotoxicity Studies – Technical Ethaboxam	
Acute gavage (range-finding, time to peak effect) Sprague-Dawley rats PMRA #2111055	Supplemental **≥300 mg/kg bw:** ↑ bright yellow urine **≥1000 mg/kg bw:** ↓ bwg **2000 mg/kg bw:** transient irregular and shallow breathing (1♂) 25 min post-dose but resolved by 1 h post-dose, select animals showed reduced arousal in the arena up to 6 h post-dose
Acute gavage Sprague-Dawley rats PMRA #2111056	NOAEL = 300/1000 mg/kg bw/day LOAEL = 1000/2000 mg/kg bw/day **≥1000 mg/kg bw:** ↓ motor activity (day 1, rearing counts) (♀) **2000 mg/kg bw:** ↓ bwg (overall ♂ 10%, ♀ 16%); ↓ fc (♂ 11%) **No evidence of neurotoxicity.**
90-day oral dietary Sprague-Dawley rats PMRA #2117990	NOAEL = 43/50 mg/kg bw/day LOAEL = 106/122 mg/kg bw/day **106/122 mg/kg bw/day:** ↓ fc; ↓ bw (11%), bwg (18%) (♂) **No evidence of neurotoxicity.**
Special Studies (non-guideline) – Technical Ethaboxam	
Acute oral toxicity, gavage, Irwin dose range-finding study CD-1 mice PMRA #2111100	Supplemental No treatment-related mortalities or clinical signs.

Immunotoxicity, Jerne PFC assay (range-finding), dietary Sprague-Dawley rats PMRA #2111106	Supplemental **≥40 mg/kg bw/day:** ↓ fc (week 1 only at LD, non-adverse at LD) **≥75 mg/kg bw/day:** ↓ bw, bwg (bw loss at HD) **155 mg/kg bw/day:** ↓ adrenal and thymus wts No treatment-related effect on PFC/10^6 viable cells, PFC/spleen or viable cells/spleen.
Immunotoxicity, Jerne PFC assay, dietary Sprague-Dawley rats PMRA #2111107	**Systemic** NOAEL = 21 mg/kg bw/day LOAEL = 52 mg/kg bw/day **Immunotoxicity** NOAEL = 52 mg/kg bw/day LOAEL = 121 mg/kg bw/day **≥52 mg/kg bw/day:** ↓ bw, ↓ bwg, ↓ fc, ↓ abs. spleen wt (♂) **121 mg/kg bw/day:** ↓ abs. adrenal and abs. thymus wts (♂) No treatment-related effect on PFC/10^6 viable cells, PFC/spleen or viable cells/spleen.
90-day dietary – hormone measurements, genital tract pathology Sprague-Dawley rats PMRA #2111054	Supplemental **≥34.8 mg/kg bw/day:** ↓ bw, ↓ bwg (includes periods of bw loss), ↓ fc, ↓ fe, ↓ abs. epididymis wts, ↑ cellular debris in ducts of epididymis, ↑ unilateral or bilateral germ cell depletion/degeneration in testis **114.3 mg/kg bw/day:** ↓ testosterone (Days 7, 14, 28, recovery by Day 91), ↑ LH (Day 91 only), ↑ follicle-stimulating hormone (Day 91 only), ↓ epididymal wt, testes wt, ↓ abs. prostate wts, ↑ small epididymis, ↑ small and flaccid testes, ↑ epididymal inflammation, ↑ reduced number of spermatozoa, ↑ bilateral presence of multinucleated giant cells of testis, ↑ bilateral interstitial cell hyperplasia in testis, ↑ absent spermatozoa in epididymis (1♂), ↑ ductular multinucleated giant cells in epididymis (1♂)
Proposed MOA for Leydig cell tumours Sprague-Dawley rats PMRA #2111013	MOA sequence of key events for testicular interstitial cell adenomas: i) interruption of spermatid differentiation, ii) decreases in testosterone (T) levels and concomitant increases in luteinizing hormone (LH) levels, iv) sustained increased in interstitial cell proliferation progressing to hyperplasia, v) tumour formation. In general, it is considered plausible that this sequence of key events could lead to the formation of this tumour type. An assessment of the weight-of-evidence resulted in the following inconsistencies and information gaps: • At the tumorigenic dose of 300 ppm, there were no data available for T or LH levels, and there was no evidence of interstitial cell hyperplasia in the testes, even after 2 years of treatment. • At 650 ppm, there was no evidence of altered T and LH levels within 90 days, and there were no data available for time points beyond 90 days; it is unclear whether hormone disruption occurs, and is sustained, at this dose level. • At 650 ppm, treatment-related interstitial cell proliferation was not observed, even after after 2 years of treatment. • Increased LH levels and interstitial cell hyperplasia were demonstrated at 2000

	ppm with 90 days of treatment, but the relevance of this dose level is uncertain because it is more than 3-fold in excess of the highest tumourigenic dose investigated in the chronic toxicity/oncogenicity study in rats. • No reversibility data were available for any of the key events. Overall, there was weak cohesion between the tumour response and the key events at 300 and 650 ppm, particularly beyond the 90 days of exposure. There was insufficient evidence available to support the proposed MOA framework.
Telemetric evaluation of cardiovascular effects, oral, capsule Beagle dogs PMRA #2111101	Supplemental **≥200 mg/kg bw:** ↓ fecal consistency, ↑ emesis **1000 mg/kg bw:** ↑ systolic blood pressure 6-12 h post-dose, ↑ RR intervals at 0.5 h post-dose
Effects on testosterone production in vitro (enzyme-linked immunoassay, ELISA) Human adrenocortical cells PMRA #2111104, 2351487	Supplemental No cytotoxicity (≥80% cell viability up to 100 μM) No treatment-related effect on in vitro testosterone production under the conditions of the assay.
Effects on human estrogen receptor alpha (hERα) and human androgen receptor (hAR) using in vitro Luciferase reporter gene assays HeLa9903, 4-11 and 11-4 cells (human uterine cervical carcinoma cells) PMRA #2111102, #2351486	Supplemental No treatment-related agonistic or antagonistic effects on hERα or hAR in vitro, up to 1 μM, the highest concentration tested 10 μM ethaboxam: ↓ transcriptional activity of constitutively expressed luciferase (receptor-independent control assay)
Toxicity Studies - Transformation product LGC-35523 [N-(cyano-thiophen-2-yl-methyl)-oxalamic acid]	
Acute oral, gavage CD rats PMRA #2111015	LD_{50} > 5000 mg/kg bw (♀)
28-day, oral, dietary Sprague-Dawley rats PMRA #2111027	Supplemental **1104.1/1155.8 mg/kg bw/day:** ↓ fc; ↓ bw, bwg (♂); ↑ cholesterol (♀)

Bacterial reverse mutation PMRA #2111074	Negative
In vitro mammalian chromosome aberration test Human lymphocytes PMRA #2111081	Negative

Table 3 Toxicity Profile of Intego Solo Fungicide Containing Ethaboxam

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats PMRA #2111224	$\text{LD}_{50} > 5000$ mg/kg bw (♀) Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA #2111225	$\text{LD}_{50} > 5000$ mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA #2111230	$\text{LC}_{50} > 2.73$ mg/L, MMAD = 2.59 µm, GSD = 2.68 Low toxicity
Dermal irritation NZW Rabbits PMRA#2111232	$\text{MAS}_{24\text{-}72\text{ h}} = 0.11/8$, $\text{MIS}_{1\text{ h}} = 0.67/8$ (♂) Minimally irritating
Eye irritation NZW Rabbits PMRA #2111231	$\text{MAS}_{24\text{-}72\text{ h}} = 0/110$, $\text{MIS}_{1\text{ h}} = 0.67/110$ (♂) Non-irritating
Dermal sensitization (Beuhler test) Dunkin/Hartley Guinea pigs PMRA #2111234	Non-sensitizer (♂)

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Ethaboxam

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary General population	Developmental toxicity study in the rat	NOAEL = 100 mg/kg bw Body weight loss and reduced body weight gain within the first two days of dosing	100
	ARfD = 1 mg/kg bw		
Repeat dietary	24-month chronic toxicity/oncogenicity study in the rat	NOAEL = 5.5 mg/kg bw/day Male reproductive organ effects – germ cells, abnormal spermatogenesis, testes, epididymides and prostate pathology	100
	ADI = 0.055 mg/kg bw/day		
Short- to Intermediate-term dermal[2] and inhalation[3]	24-month chronic toxicity/oncogenicity study in the rat	NOAEL = 5.5 mg/kg bw/day Male reproductive organ effects – germ cells, abnormal spermatogenesis, testes, epididymides and prostate pathology	100
Cancer	Evidence of oncogenicity. A lifetime adjusted unit risk factor (q_1*) of 1.96E^{-2} was based on Leydig cell tumourigenicity in the male rat.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments. [2] An oral NOAEL was selected and a dermal absorption factor of 11% was used in route-to-route extrapolation. [3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN GRAPES		**PMRA # 2111111, 2111113, 2111116, and 2111117**	
Radiolabel Position	[^{14}C-thiazole] and [^{14}C-thiophene]		
Test Site	Mature grape plants were selected from a vineyard		
Treatment	Foliar treatment		
Total Rate	[^{14}C-thiazole] label: 5 x 234 – 274 g a.i./ha; total rate of 1260 g a.i./ha [^{14}C-thiophene] label: 5 x 242 – 294 g a.i./ha; total rate of 1293 g a.i./ha		
Formulation	Wettable powder (WP) formulation		
Preharvest interval	0, 5, 10, and 14 days for fruit and leaves		
Matrices	**PHI (days)**	**[^{14}C-thiazole]**	**[^{14}C-thiophene]**
		TRR (ppm)	**TRR (ppm)**
Fruit	0	1.83	1.56
	5	0.816	0.901
	10	0.919	0.903
	14	0.535	0.845
Leaves	0	72.9	105.7
	5	42.5	41.2
	10	39.7	45.0
	14	29.5	34.9

Metabolites Identified	Major Metabolites (>10% of the TRR)		Minor Metabolites (<10% of the TRR)	
Radiolabel Position	[^{14}C-thiazole]	[^{14}C-thiophene]	[^{14}C-thiazole]	[^{14}C-thiophene]
Grape, fruit (all PHIs)	Ethaboxam	Ethaboxam, LGC-35523	None	None
Leaves (PHI 14)	Ethaboxam	Ethaboxam	None	None

Additional metabolites (TzF1 and TpF1) were shown to be incorporated into sugar fractions. As such, it was proposed that ethaboxam is metabolized in grapes to LGC-35523 by photolytic degradation and incorporated into natural products (sugars).

The study also conducted a translocation experiment, which involved covering two bunches of grapes with polyethene bags prior to spraying. The TRR in fruit protected from application accounted for 0.137 ppm and 0.104 ppm, respectively for the thiazole and thiophene radiolabels at harvest, indicating that translocation was low.

NATURE OF THE RESIDUE IN POTATO	PMRA # 2111114
Radiolabel Position	[^{14}C-thiazole] and [^{14}C-thiophene]
Test Site	In individual pots in a plastic-covered polytunnel in a fenced enclosure with impermeable floor covering
Treatment	Foliar treatment
Total Rate	[^{14}C-thiazole] label: 5 x 251 – 261 g a.i./ha; total rate of 1263 g a.i./ha [^{14}C-thiophene] label: 5 x 259 – 264 g a.i./ha; total rate of 1310 g a.i./ha
Formulation	Wettable powder (WP) formulation
Preharvest interval	0, 5, 10, and 14 days for tubers and foliage

Matrices	PHI (days)	[^{14}C-thiazole]	[^{14}C-thiophene]
		TRR (ppm)	TRR (ppm)
Tubers	0	0.037	0.020
	5	0.073	0.033
	10	0.038	0.023
	14	0.073	0.029
Foliage	0	13.8	12.1
	5	25.0	19.0
	10	11.7	15.3
	14	11.4	7.02

Metabolites Identified	Major Metabolites (>10% of the TRR)		Minor Metabolites (<10% of the TRR)	
Radiolabel Position	[^{14}C-thiazole]	[^{14}C-thiophene]	[^{14}C-thiazole]	[^{14}C-thiophene]
Tubers (0 and 5 day PHI)	None	None	Ethaboxam	Ethaboxam
Foliage (14 day PHI)	Ethaboxam	Ethaboxam	None	None

Incorporation of radiolabels into natural products was examined in the 14-day PHI tubers. Crude starch fractions were precipitated by addition of ethanol to the extracts. The fractions accounted for 41.2% of the TRR (0.030 ppm) and 42.9% of the TRR (0.012 ppm) in thiazole- and thiophene-labeled ethaboxam-treated tubers, respectively. Acid hydrolysis of the starch fractions released about 38-39% of the TRR as glucose, and derivatization of the glucose residues to glucosazone accounted for 18-23% of the TRR in tubers. Based on these results, it was proposed that ethaboxam is extensively metabolized in potatoes to carbohydrates (glucose, starch).

NATURE OF THE RESIDUE IN TOMATO	PMRA #2111115
Radiolabel Position	[^{14}C-thiazole] and [^{14}C-thiophene]
Test Site	In individual pots in a plastic-covered polytunnel
Treatment	Foliar treatment
Total Rate	3 x 200 g a.i./ha; total rate of 600 g a.i./ha
Formulation	Soluble concentrate (SC) formulation
Preharvest interval	0, 3, 14, and 21 days for fruit; 21 days for leaves, stems and roots

Matrices	PHI (days)	[^{14}C-thiazole]	[^{14}C-thiophene]
		TRR (ppm)	TRR (ppm)
Fruit	0	0.987	1.06
	3	1.32	1.47
	7	1.13	0.956
	14	1.08	1.28
	21	0.399	0.685
Leaves	21	55.2	54.6
Stems	21	6.85	5.3
Roots	21	0.700	1.06

Metabolites Identified	Major Metabolites (>10% of the TRR)		Minor Metabolites (<10% of the TRR)	
Radiolabel Position	[^{14}C-thiazole]	[^{14}C-thiophene]	[^{14}C-thiazole]	[^{14}C-thiophene]
Fruit (all PHIs)	Ethaboxam	Ethaboxam	None	LGC-35523
Leaves (PHI 21)	Ethaboxam	Ethaboxam	None	None

It was proposed that ethaboxam is metabolized in tomatoes to LGC-35523.

The study also conducted a translocation experiment, which involved covering three trusses with polyethene bags prior to spraying. The TRR in fruit protected from application accounted for 0.053 ppm and 0.016 ppm, respectively for the thiazole and thiophene radiolabels at harvest, indicating that translocation was low.

NATURE OF THE RESIDUE IN CANOLA, CORN, SORGHUM, SOYBEAN, AND WHEAT	**PMRA # 2111256**
Radiolabel Position	[^{14}C-thiazole] and [^{14}C-thiophene]
Test Site	In planter boxes containing loam soil
Treatment	Seed treatment
Total Rate	Canola, corn, sorghum, and wheat: 7.5 g a.i./100 kg seed (nominal) 7.46 – 7.74 g a.i./100 kg seed (actual) Soybean: 10 or 15 g a.i./100 kg seed (nominal) 9.92 – 10.12 or 14.84 – 15.23 g a.i./100 kg seed (actual)
Formulation	Suspension
Preharvest interval (days after planting [DAP])	162 for canola seed, 78 for corn kernel plus cob with husks removed (K+CWHR), 104 for corn forage, 119 for corn grain and stover, 78 for sorghum forage, 146 for sorghum grain and stover, 22 for wheat forage, 150 for wheat hay, 171 for wheat grain and straw, 63 for soybean forage, 85 for soybean hay, 114 for soybean succulent seed and pod, and 139 for mature soybean seed

Matrices	Nominal Application rate (g a.i./100 kg seed)	DAP (days)	[^{14}C-thiazole]	[^{14}C-thiophene]
			TRR (ppm)	TRR (ppm)
Canola seed	7.5	162	<0.005, <0.005	<0.005, <0.005
Corn K+CWHR	7.5	78	<0.005, <0.005	<0.005, <0.005
Corn forage	7.5	104	<0.005, <0.005	<0.005, <0.005
Corn grain	7.5	119	<0.005, <0.005	<0.005, <0.005
Corn stover	7.5	119	<0.005, <0.005	<0.005, <0.005
Sorghum forage	7.5	78	<0.005, <0.005	<0.005, <0.005
Sorghum grain	7.5	146	<0.005, <0.005	<0.005, <0.005
Sorghum stover	7.5	146	<0.005, <0.005	<0.005, <0.005
Wheat forage	7.5	22	<0.005, **0.006**	<0.005, <0.005
Wheat hay	7.5	150	<0.005, <0.005	<0.005, <0.005
Wheat grain	7.5	171	<0.005, <0.005	<0.005, <0.005

Wheat straw	7.5	171	<0.005, <0.005	<0.005, <0.005
Soybean forage	10	63	<0.005, **0.006**	<0.005, <0.005
Soybean hay	10	85	**0.023, 0.006 (0.025)**	**0.009, 0.007**
Soybean, succulent seed with pod [1]	10	114	<0.005, <0.005	<0.005, <0.005
Soybean, succulent seed without pod [1]	10	114	<0.005, <0.005	<0.005, <0.005
Soybean , succulent pod without seed [1]	10	114	<0.005, <0.005	<0.005, <0.005
Soybean mature seed	10	139	<0.005, <0.005	<0.005, <0.005
Soybean forage	15	63	**0.005, 0.007**	<0.005, <0.005
Soybean hay	15	85	**0.008, 0.013**	**0.008, 0.018 (0.018)**
Soybean, succulent seed	15	114	<0.005, <0.005	<0.005, <0.005
Soybean, succulent pod	15	114	<0.005, <0.005	<0.005, <0.005
Soybean , succulent seed with pod [1]	15	114	<0.005, <0.005	<0.005, <0.005
Soybean mature seed	15	139	<0.005, <0.005	<0.005, <0.005

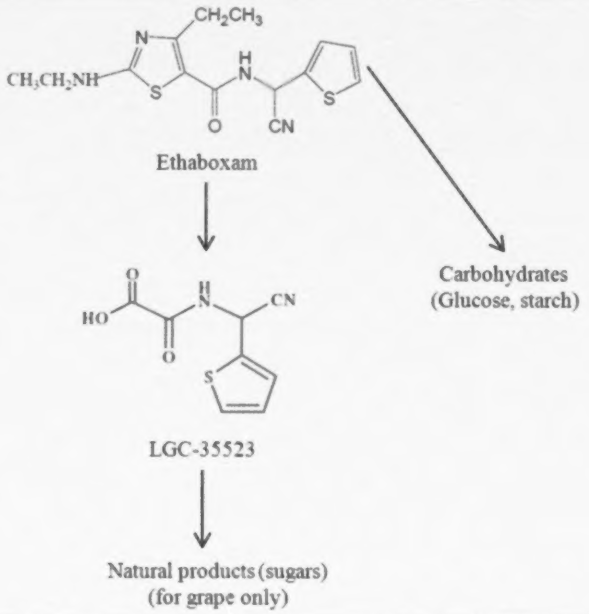
All TRR were determined by combustion/LSC, except for the TRR in brackets for soybean hay, which were determined by summing extractable and nonextractable radioactivity. **Quantifiable residues are bolded.**

[1] TRR calculated based on the sum of the combustion analysis results for succulent seed and pod.

Residues in soybean hay were extracted, and were characterized/identified using high performance liquid chromatography (HPLC). Extraction procedures extracted the majority of the residues (54-57% of the TRR extractable). Residues eluted at the retention time of ethaboxam, but TRR were <0.001 ppm (0.8 – 2.1% of the TRR), of which the remaining extractable radioactivity was characterized as unknown components or regions (each ≤19.0% of the TRR or ≤0.004 ppm) or unresolved radioactivity (≤9.5% of the TRR, ≤0.002 ppm). No further attempts were made to identify these metabolites.

Proposed Metabolic Scheme in Plants

The proposed metabolite pathway for ethaboxam in grapes and tomatoes involves cleavage of the thiazole ring to form LGC-35523, an α-keto carboxylic acid. In grapes, LGC-35523 is further metabolized into natural products (sugars). In potatoes, ethaboxam is metabolized into carbohydrates (sugars, starch). However, in the investigation of the metabolism of ethaboxam in canola, corn, sorghum, wheat, and soybean after seed treatment, only the parent was identified.



NATURE OF THE RESIDUE IN LAYING HEN	**PMRA #2165444**

Twenty laying hens were dosed orally with [^{14}C-thiazole]-ethaboxam or [^{14}C-thiophene]-ethaboxam at 10.6 ppm by gelatin capsule once daily for seven consecutive days. Samples of excreta were collected daily. Samples of eggs were collected twice daily. The hens were euthanized 20-22 hours after administration of the final dose, and the following samples were collected: muscle (breast and thigh), fat (omental and subcutaneous), liver, and GI tract (with contents).

Matrices	**[^{14}C-thiazole]**		**[^{14}C-thiophene]**	
	TRR (ppm)	**% of Administered Dose***	**TRR (ppm)**	**% of Administered Dose***
Excreta	--	92.8	--	93.6%
Muscle (thigh)	0.022	0	0.048	0
Muscle (breast)	0.018	0	0.041	0
Fat (omental)	0.019	0	0.026	0
Fat (subcutaneous)	0.016	0	0.025	0
Liver	0.830	0.5	0.806	0.4
Eggs (Day 8 AM)	0.079	0.05	0.097	0.05
GI tract with contents	--	1.4	--	1.0

* As reported in study report.

Metabolites identified	**Major Metabolites (>10% of the TRR)**		**Minor Metabolites (<10% of the TRR)**	
Radiolabel Position	[^{14}C-thiazole]	[^{14}C-thiophene]	[^{14}C-thiazole]	[^{14}C-thiophene]
Muscle (thigh)	None	M2	Ethaboxam	None
Muscle (breast)	None	M2	Ethaboxam	None
Fat (omental)	None	M2	None	None
Fat (subcutaneous)	None	M2	None	None
Liver	None	None	M1, ethaboxam	M2, M1, ethaboxam
Eggs (Day 8 AM)*	M1	M2	None	M1

* Residues in day 8 AM egg samples were extracted, characterized and identified, since they had the most residues.
M1 = desethylethaboxam, M2 = a cyanoformamide

Ethaboxam, M1 and M2 were also identified in the excreta. Other residues were either characterized as polar, did not warrant further characterization, or could not be further characterized because of low recoveries after isolation/purification attempts.

NATURE OF THE RESIDUE IN LACTATING GOAT | **PMRA #2165446**

Two lactating goats were dosed orally with [^{14}C-thiazole]-ethaboxam or [^{14}C-thiophene]-ethaboxam at 10.5 ppm by gelatin capsule once daily for five consecutive days. Samples of excreta were collected daily and milk was collected twice daily. The goats were euthanized 20-22 hours after administration of the final dose, and the following samples were collected: muscle (flank and loin), fat (omental, subcutaneous and renal), kidney, liver GI tract, cage wash, bile and blood.

Matrices	**[^{14}C-thiazole]**		**[^{14}C-thiophene]**	
	TRR (ppm)	**% of Administered Dose**	**TRR (ppm)**	**% of Administered Dose**
Urine	--	16.9	--	22.7
Feces	--	52.2	--	45.8
Cage wash	--	0.1	--	0.2
Muscle (flank)	0.054	0.01	0.030	0.001
Muscle (loin)	0.051	0.02	0.029	0.001
Fat (omental)	0.039	0.01	0.027	0.01
Fat (subcutaneous)	0.059	0.00	0.036	<0.01
Fat (renal)	0.040	0.02	0.021	0.01
Kidney	0.458	0.05	0.486	0.06
Liver	1.822	1.0	1.496	1.1
GI tract with contents	--	23.2	--	8.8
Bile	6.800	0.04	3.072	0.01
Blood	0.143	--	0.083	--
Skim milk (Day 4 PM)	0.165	0.04	0.079	0.02
Milk fat (Day 4 PM)	0.543	0.01	0.199	<0.01

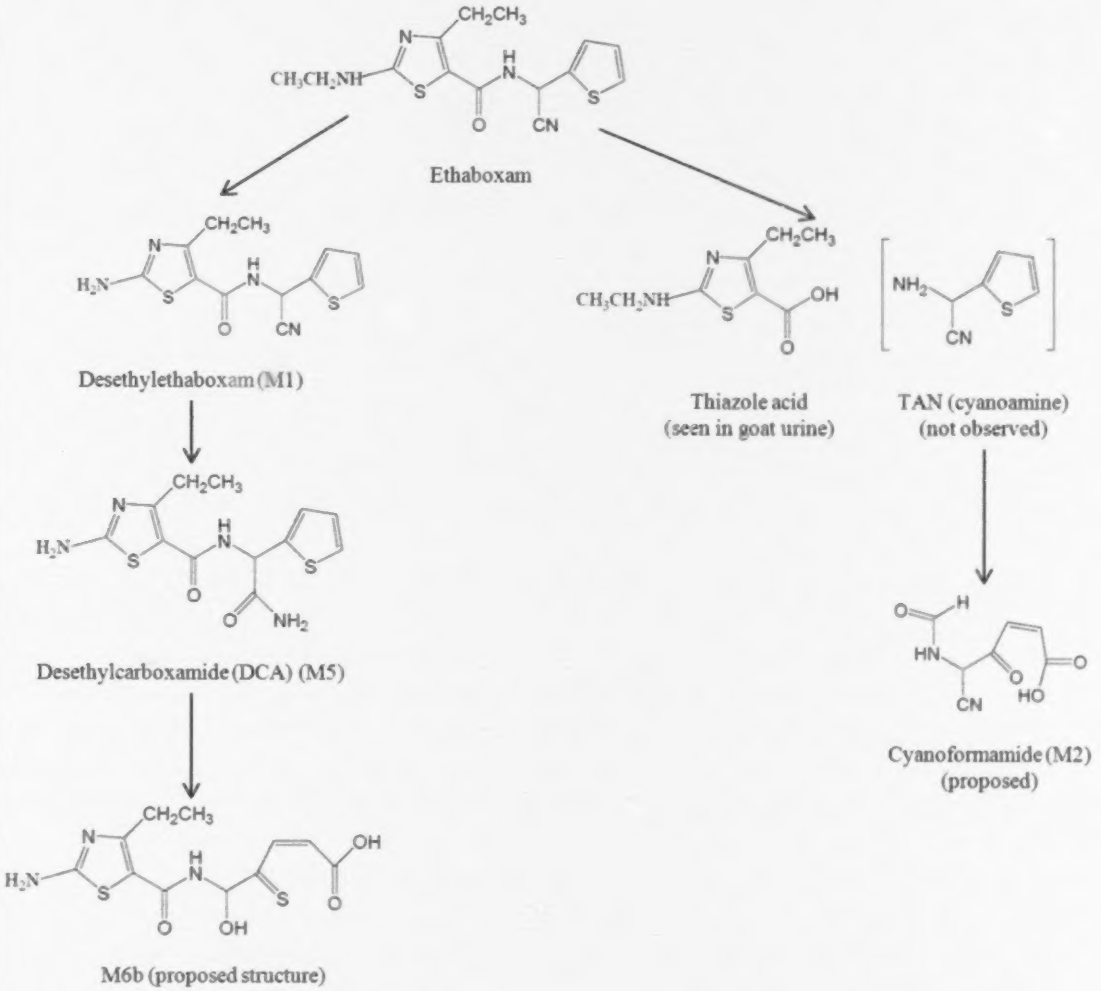
Metabolites identified	**Major Metabolites (>10% of the TRR)**		**Minor Metabolites (<10% of the TRR)**	
Radiolabel Position	[^{14}C-thiazole]	[^{14}C-thiophene]	[^{14}C-thiazole]	[^{14}C-thiophene]
Muscle (flank)	M1	M1, M2	Ethaboxam, M5	Ethaboxam
Muscle (loin)	M1	M2, M1	Ethaboxam, M5	Ethaboxam
Fat (omental)	M1, ethaboxam	Ethaboxam, M1	None	M2
Fat (subcutaneous)	M1, ethaboxam	Ethaboxam, M1	None	M2
Fat (renal)	M1, ethaboxam	Ethaboxam, M1, M2	None	M2
Kidney	M1, M5	M2	M6b, ethaboxam	M1, M5, ethaboxam, M6b,
Liver	M1	None	M6b, M5, ethaboxam	M1, ethaboxam, M5, M2, M6b
Skim milk (Day 4 PM)*	M1, M5	M1, ethaboxam, M2	Ethaboxam	M5
Milk fat (Day 4 PM)*	M1, ethaboxam	M1, ethaboxam	None	M2

* Residues in day 4 PM milk samples were extracted, characterized and identified, since they had the highest TRR.
M1 = desethylethaboxam, M2 = a cyanoformamide, M5 = desethylcarboxamide (DCA),
M6b = proposed hydroxyl carboxylic acid (see proposed metabolic scheme in livestock for structure)

Ethaboxam, M1, M2 and thiazole acid were also identified in the excreta. Other residues were either characterized as polar, did not warrant further characterization, or could not be further characterized because of low recoveries after isolation/purification attempts.

Proposed Metabolic Scheme in Livestock

The proposed metabolic pathway for ethaboxam in livestock involves cleavage of the ethyl group to form desethylethaboxam. The cyano group of M1 is then hydrolyzed to form desethylcarboxamide (DCA). It is proposed that the thiophene ring of M5 is oxidized with subsequent ring opening, and then the adjacent carbon is oxidized to form a hydroxyl carboxylic acid (M6b). The proposed metabolic pathway for ethaboxam in livestock also involves the cleavage at the amide bond to form thiazole acid and TAN. TAN is then formylated and the thiophene ring is oxidized to form M2, a cyanoformamide.


Ethaboxam

Desethylethaboxam (M1)

Desethylcarboxamide (DCA) (M5)

M6b (proposed structure)

Thiazole acid
(seen in goat urine)

TAN (cyanoamine)
(not observed)

Cyanoformamide (M2)
(proposed)

FREEZER STORAGE STABILITY	**PMRA # 2268643**

Plant matrices: Soybean seed

The freezer storage stability data indicate that residues of ethaboxam are stable at -20°C for 227 days.

CROP FIELD TRIALS ON SOYBEAN	**PMRA # 2111255**

Three field trials were conducted in 2010 in the United States. Trials were conducted in NAFTA Growing Region 5, which is representative of Canadian growing regions. Each trial consisted of one untreated plot and two treated plots. Each treated plot was grown from soybean pre-treated with Intego Solo Fungicide at either 7.5 g a.i./100 kg seed (1x approved rate) or 37.5 g a.i./100 kg (5x approved rate). Treated seed was planted 4-55 days after treatment. Seed samples were harvested at 109-147 days after planting. Only seed samples collected from the 5x approved rate plot were analyzed.

Commodity	Total Application Rate (g a.i./100 kg seed)	PHI (days)	Residue Levels (ppm)							
			n	Min. #	Max. #	LAFT *	HAFT *	Median *	Mean *	SD *
Ethaboxam										
Soybean seed	37.5	109-147	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	--

Values based on total number of samples. The study authors reported the values as <LOD (<0.005 ppm).

* Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values < LOQ are assumed to be at the LOQ.

n = number of field trials.

Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

<table>
<tr><th colspan="4">PLANT STUDIES</th></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR ENFORCEMENT
Primary crops (Crop Group 6 [except cow pea and field pea], Crop Group 15 [except rice, sorghum, and wild rice], and Crop Group 20A)
Rotational crops</td><td colspan="2">Ethaboxam</td></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR RISK ASSESSMENT
Primary crops (Crop Group 6 [except cow pea and field pea], Crop Group 15 [except rice, sorghum, and wild rice], and Crop Group 20A)
Rotational crops</td><td colspan="2">Ethaboxam</td></tr>
<tr><td colspan="2">METABOLIC PROFILE IN DIVERSE CROPS</td><td colspan="2">Grape and tomato have similar metabolic profiles (ethaboxam metabolized to LGC-35523), which are different from potato (parent converted into carbohydrates) and canola, corn, sorghum, wheat and soybean (in which only ethaboxam was identified).</td></tr>
<tr><th colspan="4">ANIMAL STUDIES</th></tr>
<tr><td colspan="2">ANIMALS</td><td colspan="2">Ruminant and Poultry</td></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR ENFORCEMENT</td><td colspan="2">Ethaboxam</td></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR RISK ASSESSMENT</td><td colspan="2">Ethaboxam</td></tr>
<tr><td colspan="2">METABOLIC PROFILE IN ANIMALS
(goat, hen, rat)</td><td colspan="2">Similar in goat and hen and different in the rat, with no cleavage of ethaboxam at the amide bond.</td></tr>
<tr><td colspan="2">FAT SOLUBLE RESIDUE</td><td colspan="2">No</td></tr>
<tr><td colspan="4">DIETARY RISK FROM FOOD AND WATER</td></tr>
<tr><td rowspan="8">Basic chronic non-cancer dietary exposure analysis
ADI = 0.055 mg/kg bw/day
Estimated chronic drinking water concentration = 0.15 μg/L</td><td rowspan="2">POPULATION</td><td colspan="2">ESTIMATED RISK
% of ACCEPTABLE DAILY INTAKE (ADI)</td></tr>
<tr><td>Food Alone</td><td>Food and Water</td></tr>
<tr><td>All infants < 1 year</td><td><1.0</td><td><1.0</td></tr>
<tr><td>Children 1–2 years</td><td><1.0</td><td><1.0</td></tr>
<tr><td>Children 3 to 5 years</td><td><1.0</td><td><1.0</td></tr>
<tr><td>Children 6–12 years</td><td><1.0</td><td><1.0</td></tr>
<tr><td>Youth 13–19 years</td><td><1.0</td><td><1.0</td></tr>
<tr><td>Adults 20–49 years</td><td><1.0</td><td><1.0</td></tr>
</table>

	Adults 50+ years	<1.0	<1.0
	Females 13-49 years	<1.0	<1.0
	Total population	<1.0	<1.0
Basic acute dietary exposure analysis, 95th percentile **ARfD = 1 mg/kg bw (general population)** **Estimated acute drinking water concentration = 1.2 µg/L**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Alone	**Food and Water**
	All infants < 1 year	<1.0	<1.0
	Children 1–2 years	<1.0	<1.0
	Children 3 to 5 years	<1.0	<1.0
	Children 6–12 years	<1.0	<1.0
	Youth 13–19 years	<1.0	<1.0
	Adults 20–49 years	<1.0	<1.0
	Adults 50+ years	<1.0	<1.0
	Females 13-49 years	<1.0	<1.0
	Total population	<1.0	<1.0
Refined cancer dietary exposure analysis **$q_1^* = 0.0196$ (mg/kg bw/day)$^{-1}$** **Estimated chronic drinking water concentration = 0.15 µg/L**	**POPULATION**	**ESTIMATED LIFETIME CANCER RISK**	
		Food Alone	**Food and Water**
	Total population	1×10^{-6}	1×10^{-6}

Table 7 Fate and Behaviour of Ethaboxam and Transformation Products in the Environment

Property	Test substance	Value[1]	Transformation products	Comments	Reference
Abiotic transformation					
Hydrolysis		20°C pH 4, DT_{50}: 181 d; pH 7, DT_{50}: stable; pH 9, DT_{50}: 152 d (SFO – combined labels)	Major: None Minor: LGC-32525 LGC-32533 LGC-32523	Hydrolysis is not an important route of transformation.	2111124 2111116 2111117

Property	Test substance	Value[1]	Transformation products	Comments	Reference
Phototransformation on soil	Ethaboxam	DT_{50} (irradiated): 11.4 d; DT_{50} (dark): 9.1 d (DFOP – combined labels) A phototransformation half-life could not be calculated as dissipation was faster in the dark controls.	Major, Irradiated: LGC-32799 Major, Dark: LGC-32799 LGC-32533 Minor, Irradiated: LGC-32533 10 unidentified compounds CO_2 Volatile organics Minor, Dark: 10 unidentified compounds CO_2	Tranformation of ethaboxam to LGC-32799 and LGC-32533 would not be specific to phototransformation. Not expected to be an important route of dissipation	2111126 2111116 2111117
Phototransformation in water	Ethaboxam	Sterile pH 7 buffer DT_{50} (irradiated): 4.5 d; DT_{50} (dark): stable (SFO – combined labels) Predicted environmental DT_{50} for ethaboxam in sterile pH 7 buffer 4.5 d for summer sunlight at 40°N latitude	Major, Irradiated: LGC-35525 Unidentified compound with a carboxilic acid functional group Major, Dark: None Minor, Irradiated: LGC-32533 LGC-32525 LGC-32787 LGC-32788 LGC-32789 LGC-32790 LGC-32791 LGC-32792 LGC-32793 LGC-32794 LGC-32795 LGC-32796 LGC-32797 LGC-32798 LGC-35523 2-thiophene carboxamide 2-thiophene carboxilic acid Minor, Dark: None	Can be an important route of dissipation for ethaboxam near the surface in water bodies.No clear decline of the transformation products was observed.	2111127 2111116 2111117
Phototransformation in air	Ethaboxam	Ethaboxam is not expected to be volatile under field conditions based on vapour pressure and Henry's law constant.			2111123

Property	**Test substance**	**Value[1]**	**Transformation products**	**Comments**	**Reference**
Biotransformation					
Biotransformation in aerobic soil	Ethaboxam	20°C Sandy loam : DT_{50}: 1.33 d; DT_{90}: 14.7 d (IORE – combined labels; representative half-life for modelling purposes: 4.44 d)	Major: CO_2 Minor: 9 to 10 compounds per label; LGC-32525 and LGC-32533 were identified. LGC-32799 and LGC-32787/LGC-32788 were tentatively identified.	Ethaboxam is non-persistent. Biotransformation in aerobic soil is an important route of dissipation for ethaboxam and its transformation products. Important concentrations of non-extractable residues were noted.	2111128 2111116 2111117
		20°C Sandy loam: DT_{50}: 0.484 d; DT_{90}: 3.08 d. (IORE – one label; representative half-life for modelling purposes: 0.929 d) Clay loam: DT_{50}: 2.41 d; DT_{90}: 32 d. (IORE – one label; representative half-life for modelling purposes: 9.64 d) Loam: DT_{50}: 0.787 d; DT_{90}: 6.2 d. (IORE – one label; representative half-life for modelling purposes: 1.87 d) 10°C Loam: DT_{50}: 3.99 d; DT_{90}: 38.8 d. (IORE – one label; representative half-life for modelling purposes: 11.7 d)	Major: CO_2 Minor: LGC-32525 LGC-32533 7 other unidentified compounds	Ethaboxam is non-persistent. Biotransformation in aerobic soil is an important route of dissipation for ethaboxam and its transformation products. Important concentrations of non-extractable residues were noted.	2111129

Property	**Test substance**	**Value**[1]	**Transformation products**	**Comments**	**Reference**
Biotransformation in anaerobic soil	Ethaboxam	20°C Sandy loam: DT_{50}: 98.7 d; DT_{90}: 412 d (DFOP– combined labels; representative half-life for modelling purposes: 135 d)	Major: 2-thiophene carboxilic acid CO_2 Minor: LGC-32525 LGC-32533 10 other unidentified compounds Volatile organics	Ethaboxam is moderately persistent. Biotransformation in anaerobic soil is a route of dissipation for ethaboxam.	2111132 2111116 2111117
		20°C Loam: DT_{50}: 290 d; DT_{90}: 962 d (SFO – thiazole label) DT_{50}: 135d; DT_{90}: 448 d (SFO – thiophene label) Sand: DT_{50}: 134 d; DT_{90}: 444 d (SFO – thiophene label) Silt loam DT_{50}: 80.3 d; DT_{90}: 267 d (SFO – thiophene label) Sandy loam DT_{50}: 106 d; DT_{90}: 352 d (SFO – thiophene label)	Major: 2-thiophene carboxilic acid LGC-32524 CO_2 Minor: LGC-32525 LGC-32533 2-ketoglutaric acid Volatile organics	Ethaboxam is moderately persistent to persistent. Biotransformation in anaerobic soil is a route of dissipation for ethaboxam.	2117991
Biotransformation in aerobic water-sediment systems	Ethaboxam	Pond water: clay loam sediment Total system DT_{50}: 22.1 d; DT_{90}: 173d (IORE – combined labels; half-life for modelling purposes: 51.9 d) Lake water:sandy loam sediment Total system DT_{50}: 6.49 d; DT_{90}: 71.5 d (DFOP – combined labels; representative half-life for modelling purposes: 28.8 d)	Major: Unidentified compound TZSd1 CO_2 Minor: LGC-32525 LGC-32533 LGC-32787 and LGC-32788 (tentatively) 4 to 5 other unidentified compounds for each label	Ethaboxam is non-persistent to slightly persistent. Biotransformation in aerobic water-sediment systems is a route of dissipation for ethaboxam.	2111131 2111116 2111117

Property	**Test substance**	**Value**[1]	**Transformation products**	**Comments**	**Reference**
Biotransformation in anaerobic water-sediment systems	Ethaboxam	River water: sand sediment Total system DT_{50}: 105 d; DT_{90}: 502 d (IORE – combined labels; representative half-life for modelling purposes: 151 d)	Major: CO_2 Minor: LGC-32524 LGC-32525 LGC-32533 2-thiophene-carboxylic acid Polar compounds	Ethaboxam is moderately persistent. Biotransformation in anaerobic water-sediment systems is a route of dissipation for ethaboxam.	2111133
Mobility					
Adsorption / desorption in soil	Ethaboxam	Five soils: K_F: 2.24 – 56.2; K_{FOC}: 457 - 1561; $K_{d\ ads}$: 1.61 – 60.6; $K_{OC\text{-}ads}$: 404 - 1684	Not tested.	Ethaboxam is classified as having low to moderate potential for mobility in soil.	2111135
Aged soil leaching	Ethaboxam	Sandy loam	Major: None Minor: LGC-32533 Tentatively identified: LGC-32787/32788 and LGC 32799. 7 other unidentified compounds.	Little mobility for ethaboxam and its transformation products in sandy loam soil further than the top 13 cm of soil layer. Compounds were detected in every soil layer and leachate. Leachate likely contained polar compounds.	2152321 2111116 2111117
Volatilization	Not required based on the low vapour pressure (8.1×10^{-5} Pa at 25°C) and Henry's law constant (3.8×10^{-3} $Pa.m^3$/mole at 20°C).				
Bioconcentration					
Bioconcentration in fish	Ethaboxam	Whole body steady state BCF: 6.1-9.8 $L.Kg^{-1}$ After 14 days of depuration of ^{14}C-residues, the concentration of ethaboxam was < LOQ	LGC-32525 LGC-32533 5 other unidentified compounds	Did not bioconcentrate in large amounts in fish under the test conditions of the study.	2111166

[1] Kinetics models: SFO = single first-order; IORE = indeterminate order rate equation; DFOP = double first order in parallel.

Table 8 Toxicity to Non-Target Terrestrial Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
Invertebrates					
Earthworm	14d-Acute	Ethaboxam 99.0% w/w	LC_{50}: >1000 mg a.i./kg dw soil EC_{50}: >1000 mg a.i./kg dw soil NOAEC: 171 mg a.i./kg dw soil Based on body weight gain	Practically non-toxic	2111143
Bee	48h-Oral	LGC-30473 99%	LD_{50} > 111.8 µg a.i./bee	Relatively non-toxic	211144
	48h-Contact		LD_{50} > 111.8 µg a.i./bee	Relatively non-toxic	211144
Birds					
Bobwhite quail	Acute	LGC-30473 99%	LD_{50}: >2000 mg a.i./kg bw Mortality: NOAEL: 2000 mg a.i./kg bw Weight gain NOEL: 1000 mg a.i./kg bw	Practically non-toxic	2111169
Zebra finch	Acute	V-10208 technical 98.9%	LD_{50}: >2000 mg a.i./kg bw NOAEL: 2000 mg a.i./kg bw Based on mortality, decreased body weight and feed comsumption	Practically non-toxic	2111170
Bobwhite quail	8d-Dietary	LGC-30473 99%	LD_{50}: >5080 mg a.i./kg diet NOAEC: 2540 mg a.i./kg diet Based on decreased body weight and feed comsumption	Practically non-toxic	2111171
	22 week-Reproduction	LGC-30473 99%	NOAEC: 993 mg a.i./kg diet[b]	N/A	2111173 2111174
Mallard duck	8d-Dietary	LGC-30473 98.9%	LD_{50}: >6065 mg a.i./kg diet NOAEC (feed consumption, 5-8 day body weight gain): 6065 mg a.i./kg diet NOAEC (0-5 day body	Practically non-toxic	2111172

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
			weight gain): 613 mg a.i./kg diet		
	21 week-Reproduction	Ethaboxam 98.9%	NOAEC: 170 mg a.i./kg diet Based on egg production and offspring hatchability and survival	N/A	2111175
Mammals					
Rat	Acute oral	Ethaboxam 99.0% w/w	LD_{50}: >5000 mg a.i./kg bw	Practically non-toxic	2111014
	Acute oral	V-10208 3.2 FS 34.4%	LD_{50}: >5000 mg end-use product/kg bw	Practically non-toxic	2111224
	28-day oral dietary	Ethaboxam 99.2%	NOAEL: 50 mg a.i./kg bw LOAEL: 100 mg a.i./kg bw Based on decreased body weight (9-36%) and body weight gain (14-56%) (♂).	N/A	2351467
	28-day oral dietary	LGC-35523 92.6%	NOAEL: 170.9/170.7 mg TP/kg bw LOAEL: 1104.1/1155.8 mg TP/kg bw Based on decreased body weight and body weight gain (14%) (♂)	N/A	2111027
	Two-generation reproduction	Ethaboxam 99.0% w/w	**Parent:** NOAEL: N/A LOAEL: N/A **Offspring:** NOAEL: 16.2/17.6 mg a.i./kg bw (♂/♀) LOAEL: 52.6/56.1 mg a.i./kg bw (♂/♀) Based on decreased offspring viability index, mean litter size (F2), live birth index (F2), body weight (8-18%), body weight gain (13-19%).	N/A	2111050-2111052 (EPA DER 2138177)
	Two-generation reproduction (range-finding)	Ethaboxam 99.0 % w/w	Reproductive toxicity at 18 mg a.i./kg bw (lowest tested dose): decreased testicular sperm counts (F0) and seminal vesicule weights (F1).	N/A	2351471

a Atkins et al.(1981) for bees and United States Environmental Protection Agency classification for others, where applicable.

b Endpoints affected: Eggs laid/pen, Eggs cracked/pen, Eggs not cracked/eggs laid (%), Eggs set/pen, Shell thickness, Eggs set/eggs laid (%), Viable embryos/pen, Viable embryos/eggs set (%), Live embryos/pen, Live embryos/viable embryos (%), No. of hatchlings/pen, No. of hatchlings/eggs laid (%), No. of hatchlings/eggs set (%), No. of hatchlings/live embryos (%), Hatchling survival/pen, Hatchling survival/eggs set (%), Hatchling survival/no. of hatchlings (%), Hatchling weight (g), Survivor weight (g), Mean food consumption (g/bird/day), Male weight gain (g), Female weight gain (g).

Table 9 Toxicity to Non-Target Aquatic Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
Freshwater species					
Daphnia magna	48h-Acute	Ethaboxam 99.0 % w/w	EC_{50}: 0.37 mg a.i./L NOAEC: 0.28 mg a.i./L Based on immobility	Highly toxic	2111146
	21d-Chronic	Ethaboxam 98.9%	NOAEC: 0.050 mg a.i./L (reproduction)[b]	N/A	2111147
Rainbow trout	96h-Acute	Ethaboxam 99.0%	LC_{50}: 2.18 mg a.i./L NOAEC: 0.14 mg a.i./L Based on sublethal effects[c]	Moderately toxic	2111159
	Xd-Chronic	No data submitted. No data required.			
Fathead minnow	96h-Acute	Ethaboxam 99.0%	LC_{50}: > 4.6 mg a.i./L NOAEC: 4.6 mg a.i./L (highest measured concentration tested)	Not toxic to highest concentration tested	2111160
	Early life stage	LGC-30473 99%	NOAEC: 0.88 mg a.i./L Based on cumulative mortality and clinical signs of toxicity[d]	N/A	2111164
Freshwater green alga	96h-Acute	LGC-30473 99.0%	EC_{50}: >3.6 mg a.i./L Based on cell density, growth rate and area under the curve.	N/A	2111176
Marine species					
Saltwater mysids	95h-Acute	V-10208 technical 98.9%	LC_{50}: 0.42 mg a.i./L NOAEC: 0.25 mg a.i./L	Highly toxic	2111154
Eastern oyster shell deposition	96h-Acute	V-10208 technical 98.9%	EC_{50}: 0.37 mg a.i./L NOAEC: < 0.027 mg a.i./L	Highly toxic	2111156
Sheepshead minnow	96h-Acute	V-10208 technical 98.9%	LC_{50}: > 3.1 mg a.i./L NOAEC: 3.1 mg a.i./L (highest measured concentration tested)	Not toxic to highest concentration tested	2111161
	Early life stage	V-10208 technical 98.9%	NOAEC: 0.17 mg a.i./L Based on length, wet and dry weights	N/A	2111165

a United States Environmental Protection Agency classification, where applicable

b Endpoints affected: time to first brood release, total offspring produced, and total offspring produced per reproductive day (successful birth rate).

c Hyperventilation, irregular swimming, lethargy, loss of equilibrium, exophthalmia, and increased pigmentation.

d Curvature of the spine, inactivity, loss of equilibrium, and moribund condition.

Table 10 Screening Level Risk Assessment on Non-target Species Other than Birds and Mammals

Organism	Exposure	Endpoint value	EEC	RQ	Risk
Invertebrates					
Earthworm	Acute	500 mg a.i./kg soil	0.01 mg a.i./kg soil	< 0.00002	< LOC
Bee	Acute oral	> 111.8 µg a.i./bee	0.29 µg a.i./bee	< 0.003	< LOC

Table 11 Endpoints used in the risk assessment and the uncertainty factors applied

Taxonomic group	Exposure	Endpoint	Uncertainty factor
Earthworm	Acute	LC_{50}	0.5
Bee	Acute contact	LC_{50}	1
Birds	Acute	LD_{50}	0.10
	Chronic	NOEL	1
Mammals	Acute	LD_{50}	0.10
	Chronic	NOEL	1
Aquatic invertebrates	Acute	EC_{50}	0.5
	Chronic	NOEC	1
Fish	Acute	LC_{50}	0.10
	Chronic	NOEC	1
Amphibians	Acute	Fish LC_{50}	0.10
	Chronic	Fish NOEC	1
Algae		EC_{50}	0.5

Table 12 Screening Level Risk Assessment on Non-Target Terrestrial Birds and Mammals Species

	Study Endpoint (mg a.i./kg bw/day / UF)	EDE (mg a.i./kg bw/day)	RQ	Risk
Small bird (0.02 kg)				
Acute	200.00	19.071	0.10	< LOC
Reproduction	21.83	19.071	0.87	< LOC
Medium bird (0.10 kg)				
Acute	200.00	14.980	0.07	< LOC
Reproduction	21.83	14.980	0.69	< LOC
Large bird (1.00 kg)				
Acute	200.00	4.367	0.02	< LOC
Reproduction	21.83	4.367	0.20	< LOC
Small mammals (0.015 kg)				
Acute	500.00	10.898	0.02	< LOC
Reproduction	16.20	10.898	0.67	< LOC
Medium mammals (0.035 kg)				
Acute	500.00	9.373	0.02	< LOC
Reproduction	16.20	9.373	0.58	< LOC
Large mammals (1.00 kg)				
Acute	500.00	5.161	0.01	< LOC

	Study Endpoint (mg a.i./kg bw/day / UF)	EDE (mg a.i./kg bw/day)	RQ	Risk
Reproduction	16.20	5.161	0.32	< LOC

Table 13 Screening Level Risk Assessment on Non-Target Aquatic Species

Organism	Exposure	Endpoint value	EEC	RQ	Risk
Freshwater species					
Daphnia magna	Acute	0.185 mg a.i./L	0.0028 mg a.i./L	0.015	< LOC
	Chronic	0.05 mg a.i./L	0.0028 mg a.i./L	0.056	< LOC
Rainbow trout	Acute	0.218 mg a.i./L	0.0028 mg a.i./L	0.013	< LOC
Fathead minnow	Acute	> 0.46 mg a.i./L	0.0028 mg a.i./L	< 0.006	< LOC
	ELS	0.88 mg a.i./L	0.0028 mg a.i./L	0.003	< LOC
Amphibians (using the most sensitive fish endpoint as surrogate data)	Acute	0.218 mg a.i./L	0.015 mg a.i./L	0.069	< LOC
	ELS	0.88 mg a.i./L	0.015 mg a.i./L	0.017	< LOC
Freshwater alga	Acute	0.16 mg a.i./L	0.0028 mg a.i./L	0.017	< LOC
Marine species					
Crustacean	Acute	0.21 mg a.i./L	0.0028 mg a.i./L	0.013	< LOC
Mollusk	Acute	0.185 mg a.i./L	0.0028 mg a.i./L	0.015	< LOC
Sheephead minnow	Acute	> 0.31 mg a.i./L	0.0028 mg a.i./L	< 0.009	< LOC
	ELS	0.17 mg a.i./L	0.0028 mg a.i./L	0.016	< LOC

Table 14 Toxic Substances Management Policy Considerations – Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		
Predominantly anthropogenic[2]	Yes		
Persistence[3]:	Soil	Half-life ≥ 182 days	Range of DT_{50} at 20°C: 0.5 to2.4 d Range of t_R[a] at 20°C: 0.9 to 9.6 d (IORE) DT_{50} at 10°C: 4 d $t_{1/2}$ at 10°C: 11.7 d (IORE)
	Water	Half-life ≥ 182 days	Aerobic (total system) DT_{50}: 6.5 to 22.1 d $t_{1/2}$: 28.8 (DFOP) to 51.9 d (IORE) Anaerobic (total system) DT_{50}: 105 d $t_{1/2}$: 151 d (IORE)
	Sediment	Half-life ≥ 365 days	$t_{1/2}$: 80.3 to 135 d (SFO)
	Air	Half-life ≥ 2 days or evidence of	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur

TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**		**Active Ingredient Endpoints**
		long range transport	based on the vapour pressure (8.1×10^{-5} Pa) and Henry's Law Constant (3.8×10^{-3} $Pa.m^3/mole$).
Bioaccumulation[4]	$\log K_{OW} \geq 5$		2.9
	$BCF \geq 5000$		BCFs: 6.1 to 9.8 L/kg
	$BAF \geq 5000$		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.
[1] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (in other words, all other TSMP criteria are met). [2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases. [3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) then the criterion for persistence is considered to be met. [4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, $\log K_{OW}$). [a] t_R = representative $t_{1/2}$ from non-linear, multi-compartment kinetic models.			

Table 15 Summary of Fungicide Alternatives for the Uses Supported with Intego Solo Fungicide

Seed rot / Pre-emergence damping-off caused by *Pythium* spp. on cereal grains*
Active ingredient (Fungicide Resistance Action Committee Code)
difenoconazole (3) + metalaxyl (4)
difenoconazole (3) + metalaxyl-M (4)
difenoconazole (3) + metalaxyl-M and S-isomer (4)
difenoconazole (3) + metalaxyl-M and S-isomer (4) + sedaxane (7)
prothioconazole (3) + tebuconazole (3) + metalaxyl (4)
prothioconazole (3) + metalaxyl (4) + penflufen (7)
tebuconazole (3) + metalaxyl (4)
tebuconazole (3) + thiram (M3)
triticonazole (3) + thiram (M3)
carbathiin (7)
carbathiin (7) + thiram (M3)
Seed rot / pre-emergence damping-off caused by *Pythium* spp. on corn
Active ingredient (Fungicide Resistance Action Committee Code)
difenoconazole (3) + metalaxyl-M (4)
difenoconazole (3) + metalaxyl-M and S-isomer (4)
prothioconazole (3) + metalaxyl (4) + penflufen (7)
metalaxyl-M and S-isomer (4)
metalaxyl-M and S-isomer (4) + fludioxonil (12)
azoxystrobin (11)

Seed rot / pre-emergence damping-off caused by *Pythium* spp. on legume vegetables
Active ingredient (Fungicide Resistance Action Committee Code)
prothioconazole (3) + metalaxyl (4) + penflufen (7)
metalaxyl-M and S-isomer (4)
metalaxyl (4) + trifloxystrobin (11)
metalaxyl-M and S-isomer (4) + fludioxonil (12)
carbathiin (7) + thiram (M3)
Trichoderma harzianum Rifai strain KRL-AG2 (NC)
Early-season root rot caused by *Phytophthora sojae* on soybean
Active ingredient (Fungicide Resistance Action Committee Code)
prothioconazole (3) + metalaxyl (4) + penflufen (7)
metalaxyl-M and S-isomer (4)
metalaxyl-M and S-isomer (4) + fludioxonil (12)
Early-season root rot caused by *Aphanomyces euteiches* on legume vegetables
No fungicides registered.
Seed rot / pre-emergence damping-off caused by *Pythium* spp. on the rapeseed subgroup
Active ingredient (Fungicide Resistance Action Committee Code)
difenoconazole (3) + metalaxyl-M and S-isomer (4) + fludioxonil (12)
metalaxyl-M and S-isomer (4)
metalaxyl (4) + carbathiin (7) + trifloxystrobin (11)
metalaxyl (4) + carbathiin (7) + thiram (M3)
carbathiin (7) + thiram (M3)

*except corn, rice sorghum and wild rice

Table 16 Use (Label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Cereal grains (except corn, rice, sorghum and wild rice): control of pythium seed rot and pre-emergence damping-off at 13.0-17.0 mL/100 kg seed.	Supported. Disease name will be amended as follows: Seed rot and pre-emergence damping-off caused by *Pythium* spp.
Corn: control of pythium seed rot and pre-emergence damping-off at 13-19.6 mL/100 kg seed.	Supported. Disease name will be amended as follows: Seed rot and pre-emergence damping-off caused by *Pythium* spp.
Legume vegetables: control of pythium seed rot and pre-emergence damping-off at 19.6 mL/100 kg seed.	Supported. Disease name will be amended as follows: Seed rot and pre-emergence damping-off caused by *Pythium* spp.
Legume vegetables: suppression of early-season phytophthora root rot at 19.6 mL/100 kg seed.	Supported on soybean only, as the disease is host-specific to soybean. Disease name will be amended as follows: Early-season root rot caused by *Phytophthora sojae*. Confirmatory value information is required, as no assessments were made on soybean roots.

Legume vegetables: suppression of early-season aphanomyces root rot at 19.6 mL/100 kg seed.	Supported. Disease name will be amended as follows: Early-season root rot caused by *Aphanomyces euteiches*.
Rapeseed subgroup: control of pythium seed rot and pre-emergence damping-off at 13-19.6 mL/100 kg seed.	Supported. Disease name will be amended as follows: Seed rot and pre-emergence damping-off caused by *Pythium* spp.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Ethaboxam is a new active ingredient which is concurrently being registered in Canada and the United States. MRLs were proposed for ethaboxam in Canada; however, American tolerances are not to be promulgated since the use of ethaboxam on the requested crops was considered a non-food use. Currently, there are no Codex MRLs[9] listed for ethaboxam in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

Table 1 compares the MRLs proposed for ethaboxam in Canada with corresponding American tolerances and Codex MRLs. American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food website, by pesticide or commodity.

Table 1 Comparison of Canadian MRLs and American Tolerances (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)
Crop Group 6 – Legume Vegetables (Succulent or Dried) (except cowpea and field pea)	0.02	Not established
Crop Group 15 – Cereal Grains (except rice, sorghum, and wild rice)	0.02	Not established
Crop Subgroup 20A – Rapeseed	0.02	Not established

The MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

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[9] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2111001	2011, Product Identity and Composition of Ethaboxam Technical, Description of Materials Use to Produce Ethaboxam Technical, Description of Production Process for Ethaboxam Technical, Discussion of Formation of Impurities for Ethaboxam Technical, DACO: 2.1
2244647	2012, Ethaboxam Technical: Product Identity and Composition, Description of Materials Used, Description of Production Process and Discussion of Formation of Impurities, DACO: 2.11.1, 2.11.2, 2.11.3, 2.11.4
2244650	2012, Enforcement Analytical Method for Determination of Ethaboxam in Ethaboxam Technical, DACO: 2.13.1,2.13.2
2244654	2012, Enforcement Analytical Method for Determination of Production Impurities LGC-32525, LGC-32527, and LGC-32529 in Ethaboxam Technical, DACO: 2.13.1,2.13.2
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2.0 Human and Animal Health

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3.0 Environment

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4.0 Value

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B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

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